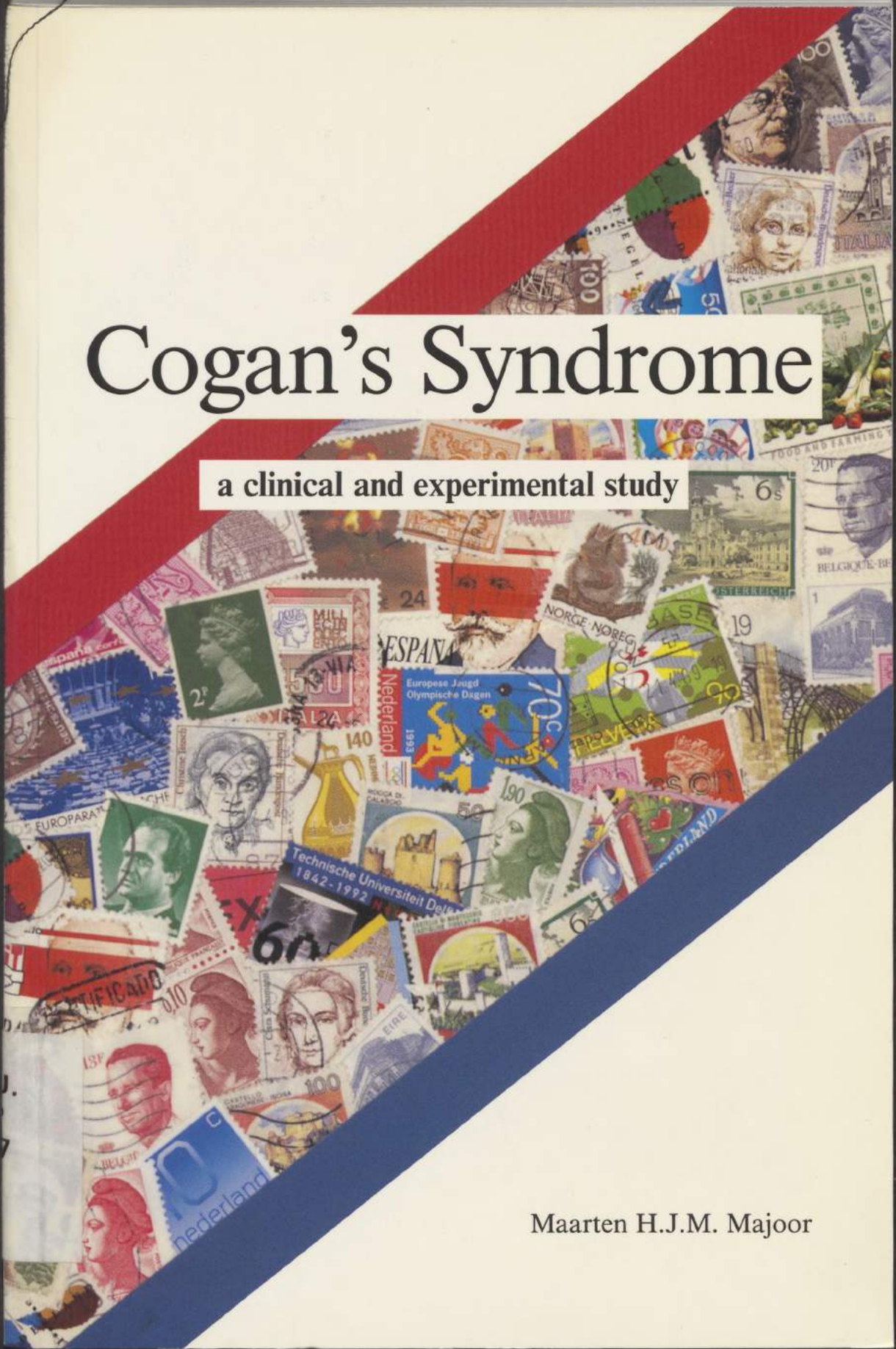
Cogan's Syndrome

a clinical and experimental study



Maarten H.J.M. Majoor

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FRONT COVER ILLUSTRATION: Stamps used by the colleagues participating in the West European study

Cogan's Syndrome

A clinical and experimental study

Het syndroom van Cogan

Een klinische en experimentele studie

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de Rector Magnificus Prof. Dr. J.A. van Ginkel
ingevolge het besluit van het College van Dekanen
in het openbaar te verdedigen op
dinsdag 10 mei 1994 des namiddags te 2.30 uur

door

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geboren op 7 december 1957 te Nijmegen

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STELLINGEN

1. Het typische syndroom van Cogan (CS) is een ziektebeeld met een eigen entiteit, gekenmerkt door welomschreven oogheelkundige en audiovestibulaire afwijkingen.

2. Het gehoorverlies bij CS is gelocaliseerd in de cochlea.

3. De pathogenese van de labyrintaire symptomen bij CS is waarschijnlijk een locale autoimmuun gemedieerde vasculitis met een eventueel secundaire endolymphatische hydrops.

4. Indien CS een autoimmuun gemedieerde ziekte is, dan vind de ontstekingsreactie op zeer locaal niveau plaats (oog en oor).

5. Als stelling (4) juist is dan is het de moeite waard te onderzoeken of in het oog en het oor het zelfde antigeen betrokken is.

6. Het is gerechtvaardigd vraagtekens te zetten bij de meeste bevindingen van histopathologische studies van het humane rotsbeen omdat het schier onmogelijk is te perfunderen en te fixeren, voordat weefselverval opgetreden is.

7. In de reconstructieve oorchirurgie is ook in het AIDS-tijdperk gebruik van allogene transplantaten verantwoord, mits de juiste selectiecriteria en conserveringsmethoden worden toegepast.
MHJM Majoor et al., Ned Tijdschr Geneeskd 137:1708-11, 1993.

8. Bij de neus-operatie volgens een zogenaamde "external approach" lijkt het onverstandig allogene transplantaten in de columella te gebruiken, aangezien een eventuele afstotingsreactie desastreuze esthetische gevolgen kan heeft.

9. Na sterilisatie maakt 40% van het aantal mannen antistoffen tegen de eigen spermatozoën. Het is merkwaardig dat dit geen autoimmuunziekte induceert.

10. Beeldverhalen van hoge kwaliteit zijn voor de ontwikkeling van humor bij het kind onontbeerlijk.

11. Het wonderlijke van afschuwelijke gebeurtenissen is dat je er zo gezellig over na kunt praten.

12. Alleen als het gesneeuwd heeft lijkt het wel mee te vallen met de vervuiling.

13. De hypocrisie van regeren: subsidiëren van de tabakscultuur en inkrimpen van de gezondheidszorg.
(vrij naar Prof. Dr G.J. Hordijk)

14. De zogenaamde ruimte-auto's wekken de illusie ruim te zijn, terwijl het opgeblazen ontwerpen zijn die nodeloze hoeveelheden lucht verplaatsen.

Maarten M.J.M. Majoor, Laren

Aan al die hier mijn queeste leest, weet,
dat dit een *proef*-schrift heet.

In nagedachtenis aan mijn vader
Opgedragen aan Mègy

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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

1- Introduction
2- Outline of the study

1. Introduction

The earliest description of what is currently known as Cogan's syndrome (CS), was published as a case of "Menière's disease complicated by recurrent interstitial keratitis," by Mogan and Baumgartner in 1934. Later in 1945, Cogan reported four cases with "nonsyphilitic interstitial keratitis associated with vertigo, tinnitus, or hearing loss." In 1949 he added four more cases. This condition has become known as "Cogan's syndrome" (CS).

Most patients are young people with often vague general symptoms. Within days to weeks they develop mostly bilateral keratitis and sensorineural hearing loss, with tinnitus, vertigo and dysbalance with nausea and vomiting. These ailments are often accompanied by nonspecific findings such as fever, weight loss, fatigue, head and neck discomfort, and commonly arthralgias, myalgias and abdominal discomfort.[4,5]

In recent years a distinction has been made by certain authors between typical (TCS) and atypical Cogan's syndrome (ACS), because of the great variety of (more or less serious) symptoms. Typical Cogan's syndrome is defined by the original criteria of Cogan, whereas atypical Cogan's syndrome is defined as a condition with audiovestibular manifestations, with or without corneal involvement and other ocular findings.[4,7,8]

Up till now, 187 cases have been described in the literature. Nine papers[2-10] reported a small series of cases, whereas the other publications mostly dealt with 1 or 2 cases.

The aetiology and pathogenesis of CS is not well understood. Various papers have addressed the question whether CS represents a vasculitis.[11-13] In 1953, Oliner et al. were the first to describe a giant-cell angiitis in CS. Vollertsen et al.[5] found a histopathologically confirmed vasculitis in 2 of the 18 cases. On the other hand, most other authors could not find any signs in the biopsies studied.[14,15]
Several authors have suggested that CS is an autoimmune disease.[4,16-18] This supposition is based on rather nonspecific findings, such as the progressively bilateral character of the eye and ear symptoms, the high erythrocyte sedimentation rate, the association with systemic disorders, and the finding that symptoms improve upon glucocorticoid therapy. Nevertheless, the evidence for the assumption is limited. In autoimmune diseases, circulating autoantibodies against (substances of) the affected tissue are present in a majority of the affected patients. This is not the case in CS.

2. Outline of this study

Attempts to form a reliable diagnosis of CS and to start a successful therapy are seriously hampered by the erratic symptomatology of this curious syndrome. In order

to recommend diagnostic tests and more effective treatment, a better understanding of the aetiopathogenesis of the syndrome is needed.

To this end, the following studies were carried out:

1. In Chapter 2, the differential diagnosis of CS is critically analyzed and a working definition of typical (TCS) and atypical Cogan's syndrome (ACS) is proposed. The clinical histopathological and immunological characteristics of CS are discussed in Chapter 3. The question whether CS is a vasculitis, an autoimmune syndrome or a combination of both is addressed.

2. A retrospective study of 98 cases of TCS and ACS in Western Europe. With the help of colleagues from 68 West European clinics, data of 98 patients with the presumed diagnosis of CS were collected. Of these, 37 fulfilled the criteria of TCS and 22 those of ACS. The remaining 39 patients did not fulfil these criteria, or essential data were not available.
   In Chapter 4, the clinical results are reported and compared with the literature.
   In Chapter 5 the audiovestibular findings and symptoms are analysed and discussed. The therapeutical modalities are evaluated and recommendations for treatment are given.

3. In Chapter 6, an investigation of autoimmune reactivity against corneal antigens in 1 TCS and 1 ACS case are described. In both cases, corneal antibodies were found at the beginning or during an exacerbation of the disease. Serum levels of these antibodies diminished significantly after glucocorticoid therapy.
   In Chapter 7, a study on corneal autoimmunity is presented in a patient with relapsing polychondritis. Because of the interstitial corneal edema associated with corneal-guttata, ciliary, conjunctival and episcleral hyperaemia, as well as sudden bilateral sensorineural hearing loss, this case is an interesting look-a-like of CS.

4. A study on magnetic resonance imaging and computed tomography of the labyrinth is performed, and the results are presented in Chapter 8. The pathological changes in the inner ears of 2 TCS and 3 ACS patients are studied, by a combined application of these modalities, and the results are compared to the clinical findings.

In Chapter 9, conclusions are presented and recommendations are given based on the findings in the preceding chapters.

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CHAPTER 2

DIFFERENTIAL DIAGNOSIS AND DEFINITION OF COGAN'S SYNDROME

1- Introduction
2- Differential diagnosis
3- Defining typical and atypical Cogan's syndrome

1. Introduction

In 1945, Cogan reported four cases demonstrating "nonsyphilitic interstitial keratitis associated with vertigo, tinnitus, *or* hearing loss." However, as all patients demonstrated a sensorineural hearing loss, Norton and Cogan[2] later redefined this syndrome as one comprising an obligatory sensorineural hearing loss. This syndrome is currently known as Cogan's syndrome (CS).

Several authors have suggested that CS is merely a manifestation of a systemic disorder, such as polyarteritis nodosa,[3,4] and not a syndrome with its own entity. Because the clinical picture of CS is capricious, some authors have distinguished a typical and an atypical form. Typical Cogan's syndrome (TCS) is defined by the original criteria of Cogan, whereas atypical Cogan's syndrome (ACS) is defined as a condition with audiovestibular manifestations, with or without corneal involvement and ocular findings.[5-7]

In this chapter, the differential diagnosis of CS is reviewed and the definitions of its TCS and ACS forms are reappraised.

Table 1. Differential diagnosis of Cogan's syndrome.

1. Disorders with interstitial keratitis and audiovestibular symptoms, with or without systemic involvement due to infection:
   - Congenital syphilis (acquired syphilis)
   - Tuberculosis (with streptomycin therapy)
   - Herpes virus infections
   - Congenital rubella
   - Mumps
   - Influenza
   - Chlamydia infections
   - Lyme borreliosis
   - Onchocerciasis

2. Systemic diseases associated with audiovestibular symptoms, keratitis, or other ophthalmological symptoms:
   - Vasculitis
     - Polyarteritis nodosa
     - Wegener's granulomatosis
     - Behçet's syndrome
     - Giant cell arteritis
     - Takayasu's arteritis
   - Relapsing polychondritis
   - Sarcoidosis
   - Autoimmune disorders
     - Systemic lupus erythematosus
     - Rheumatoid arthritis
     - Sjögren's syndrome

2. Differential diagnosis

The differential diagnosis of CS is based on two main criteria: (1) focal, peripheral interstitial keratitis, often with typical exacerbations and remissions; and (2) audiovestibular symptoms.
Not only the eye and ear but other organ systems are also involved in this syndrome. Systemic involvement in CS and the differential diagnosis of systemic disorders resembling CS is discussed.

In view of the aforementioned criteria, we have divided the diseases relevant to the differential diagnosis into two groups (Table 1):

1. Disorders with interstitial keratitis and audiovestibular symptoms, with or without systemic involvement, due to infection;
2. Systemic diseases associated with audiovestibular symptoms, keratitis or other ophthalmological symptoms.

2.1. DISORDERS WITH INTERSTITIAL KERATITIS AND AUDIOVESTIBULAR SYMPTOMS, WITH OR WITHOUT SYSTEMIC INVOLVEMENT DUE TO INFECTION

Interstitial keratitis is an exogenously or endogenously induced inflammation of the cornea. Exogenous causes comprise bacterial and viral agents, as well as trauma. Endogenous causes may include an autoimmune reaction to intracorneal components. The term interstitial keratitis refers to non-suppurative stromal involvement, sometimes with vascularization of the cornea. Interstitial keratitis may affect the whole cornea or only a part; it may even be localized in the peripheral areas of the cornea.

Interstitial keratitis can be divided[8-10] into:

I. Suppurative interstitial keratitis;
II. Non-suppurative interstitial keratitis:
    1) Disciform (herpes zoster/simplex, mumps, varicella, variola and vaccinia);
    2) Diffuse:
        a) Bacterial,
        b) Viral,
        c) Parasitic,
        d) Unknown cause.

CS is characterized by deep, patchy corneal infiltrates. They tend to fluctuate in intensity and distribution. These infiltrates are usually located in the periphery of the cornea. They are accompanied by deep corneal vascularization, if they persist for over months. There is a non-ulcerative inflammation of the corneal parenchyma, but the epithelium and endothelium are not affected.[2] Consequently, the most important sign in the differential diagnosis of CS is a focal, peripheral interstitial keratitis with exacerbations and remissions.

Whereas the typical ophthalmological signs of CS are well established, there is little detailed information on the vestibular and the audiological pathology available.[11] While sensorineural hearing loss is always present, vertigo and tinnitus are found frequently.[6,12]

Congenital syphilis: The differentiation between CS and congenital syphilis is difficult, because the ophthalmological observations show no gross differences. In 87% of the cases interstitial keratitis is the result of congenital syphilis, and in 3-4% of the cases it is due to acquired syphilis.[8] Acquired syphilis has rarely been associated with sudden deafness.[6,12] Authors reported a false-positive serological test for syphilis in 6-8% of the patients with CS in former days.[6,13,14] Nowadays these tests are very specific and sensitive, so a positive syphilis test actually does corroborate the diagnosis of syphilis. The lipoidal antigen tests (VDRL, Venereal Disease Research Laboratories) as well as assays using *Treponema pallidum* antigen (Fluorescent *Treponemal* Antibody ABSorption; FTA-ABS) are used to detect antibodies in sera. A positive VDRL test strongly suggests infection with *Treponema pallidum*. The test is both sensitive and specific. False-positive results may be caused by autoantibodies occurring in immunologically mediated disorders.[13] A positive reaction in the FTA-ABS (false-positive results occur in about 0.18-0.26%) or the *Treponema Pallidum* Hemagglutination Assay (TPHA; false-positive results in about

Table 2. Ophthalmological and audiovestibular findings in Cogan's syndrome and congenital syphilis.

Findings	Cogan's syndrome	congenital syphilis
OPHTHALMOLOGICAL		
Cornea:	- patchy corneal infiltrates which tend to fluctuate	- milky gray tongue-shaped areas of stromal opacification
	- usually affects the periphery	- involvement of entire cornea
	- relatively mild process	- progressive and scarring
- neo-vascularization	- first perilimbal vessels, later deep corneal vascularization	- deep brush-like vessel ingrowth
- Descemet's membrane	- normal	- mostly involved
Uvea	- uveitis uncommon	- distinct uveitis
AUDIOVESTIBULAR		
Hearing	- sensorineural hearing loss, often fluctuating	- slowly developing deafness
Tinnitus	- common	- uncommon
Vertigo	- common	- no vertigo
OTHER		
Syphilis serology	- negative	- positive
Stigmata congenital syphilis	- none	- present
FOLLOW UP	- remissions and exacerbations	- progressive in three stages - initial stage - flourishing stage - regressive stage

0.07% of the cases) is strongly indicative of infection.[13]
The keratitis in syphilis and CS is similar (Table 2). Remissions and exacerbations are seen more often in CS than in syphilis. Whereas syphilis is a progressive disease with scarring of the cornea, eye disease in CS is usually a mild and reversible process.[8,10]

In both diseases, sensorineural hearing loss can be observed. A slow development of deafness without appreciable vertigo is frequently seen in syphilis. In contrast, a sudden hearing loss is seen in CS, accompanied by vertigo.[15,16,17] Congenital syphilis is characterized by Hutchinson's tooth, a saddle nose, cutaneous lesions, and other typical deformations. One case demonstrating syphilitic interstitial keratitis, progressive corneal scarring, and sudden bilateral deafness has been reported.[18]

Tuberculosis: Interstitial keratitis may also, although rarely, occur in individuals with a focus of tuberculous disease (TB) elsewhere in the body. TB is seldom seen with audiovestibular symptoms, with the exception of ototoxic effects in patients treated with streptomycin. A positive tuberculin skin test and a negative FTA-ABS test aid in forming a diagnosis.[6,8,12]

Viral infections: Many viral infections are associated with interstitial keratitis.[6,12,19] Although viral stromal keratitis is usually of a discoid type, it sometimes appears as a diffuse type of interstitial keratitis. This is known to occur in herpes, rubella, mumps, and influenza.[8] Audiovestibular symptoms may be associated with herpes and congenital rubella.
Herpes zoster infections are usually recognized by the presence of typical skin or mucosal membrane lesions. Sudden deafness with facial palsy, as part of the Ramsay Hunt syndrome, is sometimes of sensorineural but more often of mixed origin.[16,17] A dendritic keratitis is seen with punctate epithelial defects in the initial phase.[9,20]
In mumps, hearing loss is uncommon, occurring in less than 0.1% of the cases. Of these few cases, 80% involve a unilateral and 20% a bilateral sensorineural hearing loss, often with vertigo and tinnitus.[16,17] Corneal involvement usually is unilateral and appears shortly after the parotitis. Optic neuritis, transient mild interstitial keratitis, iritis, conjunctivitis, and episcleritis have been reported.[9,20]
Influenza is sometimes associated with a diffuse type of interstitial keratitis. Viral keratitis and concomitant otitis media and/or labyrinthitis may cause diagnostic confusion.
The typical course of exacerbations and remissions in CS, appropriate cultures and serological research, and the absence of other signs of viral infection are features that may be helpful.[9,16,20] On the other hand, the subepithelial nummular infiltrates in CS respond well to topical therapy with corticosteroids. Accordingly, ocular symptoms may be masked and the diagnosis CS will thus be missed.

Chlamydial infections: Peripheral corneal infiltrates may be seen in *Chlamydia trachomatis* infection, often with conjunctivitis. Inclusion bodies can be seen in the

conjunctival epithelium (TRIC, trachoma-inclusion conjunctivitis). In trachoma, healing leads to scarring of the conjunctiva. These typical signs are not seen in CS.[21] Hearing loss is usually associated with otitis media and not with sensorineural impairment.[21-24] In one case, *Chlamydia* was cultured from drainage fluid from the middle ear.[23] Haynes et al.[6] reported that 9 out of 13 patients demonstrated IgG titers to *Chlamydia trachomatis* and 4 out of 13 showed significant IgM titers. Those patients demonstrated no clinical signs of chlamydial infection. Other authors have been unable to find serological or microbiological evidence of chlamydial infection.[25-30] Darougar et al.[22] reported a case with sacro-ileitis, aortic insufficiency, aortitis, interstitial keratitis, and sensorineural hearing loss. They isolated *Chlamydia psittaci* from the conjunctiva and determined significant titers of type-specific serum anti-chlamydial antibodies. The patient died and autopsy was carried out. Unfortunately, no sections were taken from the eyes and labyrinth, and no material was obtained for detection of *Chlamydia* from the various cardiac and other lesions. Therefore, the aetiology of the otological, cardiovascular and ocular lesions is not certain.

Lyme borreliosis: Until now, only 1 patient with CS and seroreactivity to Lyme borreliosis has been described.[31] However, the tests used in this case do not fulfil the present criteria for Lyme disease, as established by the Centers for Disease Control.[32]

Onchocerciasis: Another form of stromal keratitis is exemplified by ocular onchocerciasis, a filarial disease that is a major cause of blindness in Central Africa and Central America. However, onchocerciasis is seldom seen with audiovestibular symptoms.[12]

2.2. SYSTEMIC DISEASES ASSOCIATED WITH AUDIOVESTIBULAR SYMPTOMS, KERATITIS, OR OTHER OPHTHALMOLOGICAL SYMPTOMS

Systemic diseases such as polyarteritis nodosa (PAN), Wegener's granulomatosis, Behçet's syndrome, giant cell arteritis or Takayasu's arteritis, relapsing polychondritis and sarcoidosis may be associated with audiovestibular and ocular involvement (Table 1).[12]

Polyarteritis nodosa: Robbins and Stanley[33] previously described polyarteritis nodosa as a diffuse infiltration of the small and medium-sized arteries in various parts of the body by mononuclear leukocytes and a few polymorphonuclear and eosinophilic cells. In contrast to the hearing loss seen in CS, that in patients with PAN is of the mixed type.[34] The ocular symptoms of PAN were first described by Cogan.[35] The corneal lesions consist of a furrow-like ulceration in the paralimbal regions, with moderate infiltration and vascularization. In severe cases, PAN has all the features that are classically described in the early stages of Mooren's ulcer. Already in 1951, Ingalls described bilateral uveitis and keratitis in a case with PAN. Scleral lesions

are usually present, varying from simple redness and induration to a localized necrotic slough. The pathological basis for these lesions appears to be an occlusive vasculitis. The diagnosis of PAN ultimately depends on whether biopsy demonstrates necrotizing arteritis. Studying the temporal bones of 4 reported cases of PAN, Schuknecht[37] found severe degeneration of the inner ear, indicating ischaemic lesions. In an exhaustive review of the literature on CS, Cody and Williams noted that 3 out of 27 reported cases were clinically suspect for polyarteritis nodosa.[5] Harris et al.[38] found that not one of the 101 cases of polyarteritis nodosa demonstrated ocular or audiovestibular signs. The suggested relationship between CS and polyarteritis nodosa therefore remains speculative.

Wegener's granulomatosis: Wegener's granulomatosis is a necrotizing granulomatous vasculitis affecting primarily the upper respiratory tract, lung parenchyma, and kidneys.[39] The most common otological manifestation is otitis media with effusion and conductive hearing loss. Necrotizing granulation tissue has been described in both the external and middle ear.[39] In Kempf's study, 16 out of 26 ears of patients with Wegener's granulomatosis had a mixed hearing loss, and 8 out of 26 ears showed a sensorineural hearing loss.[40] The disease has a number of interesting autoimmune characteristics, but the pathogenesis of the sensorineural hearing loss is still unknown. Ocular involvement is rare.[41]

Behçet's disease: Progressive hearing loss has been described in Behçet's disease, a chronic recurrent inflammatory multisystem condition characterized by aphthous stomatitis, iritis, and genital ulcers. The disease is uncommon in Western Europe and is associated with vasculitis, which has been suggested to be the cause of both cochlear and vestibular impairment leading to sensorineural hearing loss and vertigo.[39] A recent study[42] has reported that in 10-16% of the patients, the inner ear is affected.

Relapsing polychondritis: Relapsing polychondritis is a recurring systemic disease characterized by inflammation of mainly cartilaginous structures.[43] Conductive hearing loss may occur due to obstructive swelling of the cartilage of the meatus or involvement of the Eustachian tube cartilage inducing otitis media.[43,44] Inner ear involvement has been noted in 50% of the patients, and a few patients develop vestibular symptoms.[45] Cody and Sones[44] diagnosed in 8 out of 40 patients a sensorineural hearing loss and in 3 out of 40 cases a conductive hearing loss. Involvement of the eye has been reported in 51-72% of the patients.[43,45] The major ocular manifestations include proptosis, chemosis, episcleritis, scleritis, uveitis, conjunctivitis, keratitis, and peripheral thinning of the cornea.[43] Isaak et al.[43] found in only 2 out of 112 patients a focal white peripheral stromal infiltrate. Immunological involvement has been suggested, but the aetiology is still unknown.[39,43,44,46] Because keratitis and sensorineural hearing loss may occur, confusion with CS is possible. However, the latter does not manifest cartilaginous lesions.

Sarcoidosis: In sarcoidosis, keratitis may be seen, but it is rarely associated with audiovestibular symptoms.[12]

Systemic lupus erythematosis: In systemic lupus erythematosis (SLE) the external ear is frequently affected,[39] but relatively little is known about possible inner ear involvement. Bowman et al.[47] studied 30 patients with SLE with an 8% incidence of sensorineural hearing loss. In the eyes, keratoconjunctivitis rather than interstitial keratitis is observed.

Rheumatoid arthritis: Rheumatoid arthritis is a common systemic disease that may affect virtually every organ. Mixed hearing loss has been described. The conductive hearing loss is due to involvement of the ossicular chain in the middle ear.[48] Sensorineural hearing loss, often attributed to salicylate toxicity, has a prevalence of 29%.[48] Keratoconjunctivitis is frequently seen. Rarely, ulcerative but never interstitial keratitis may complicate rheumatoid arthritis.[39]

Sjögren's syndrome: Sjögren's syndrome is a triad of keratoconjunctivitis sicca, xerostomia, and mononuclear cell infiltration of the salivary gland. It is often associated with other autoimmune diseases such as rheumatoid artritis. Conductive hearing loss is prevalent in these cases.[39] The cornea is consistently affected by a keratoconjunctivitis rather than interstitial keratitis.

Chronic juvenile polyarteritis and spondylo-arthopathies (including ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, and the arthritis associated with inflammatory bowel disease) may demonstrate ocular lesions but there is no audiovestibular involvement.[12]
Long-term systemic medication with arsenic and gold has been associated with corneal infiltration. Many drugs (such as salicylates, antimalarial agents, aminoglycoside antibiotics, diuretics, and heavy metals) may cause audiovestibular toxicity. The side effects of these drugs in patients with rheumatic disorders or tuberculosis may lead to misdiagnosis.[12]
Finally, there is a rare disorder which can be considered in the differential diagnosis of CS. The Vogt-Koyanagi-Harada syndrome[49] consists of aseptic meningitis (50% of the patients), pigment disturbances of the hair and skin (poliosis, vitiligo), alopecia, and uveitis. Sensorineural hearing loss and tinnitus occur in 50% of the cases.[34] Since interstitial keratitis is not part of this syndrome, it can not be confused with CS.

3. Defining typical and atypical cogan's syndrome

Norton and Cogan[2] have described the typical ocular signs in CS as follows: patchy, deep corneal infiltrates which tend to fluctuate in intensity and distribution; these infiltrates are usually located in the periphery and are accompanied by deep corneal

vascularization if they persist long enough. Inflammation of the corneal parenchyma is seen (interstitial keratitis), while the epithelium and the endothelium remain unaffected. To date, the definition of this syndrome (nonsyphilitic interstitial keratitis associated with vertigo, tinnitus, and a hearing loss) has been generally accepted. In the original 4 cases described by Cogan[1] and the 15 subsequent cases of Norton and Cogan,[2] only interstitial keratitis was seen; other kinds of ocular inflammation were not observed. The key to diagnosing CS is to verify the presence of this type of interstitial keratitis, which is focal and peripheral. Because of the typical exacerbations and remissions, repeated examinations may be necessary to obtain this confirmation.

The qualification of "ACS" has been used for different symptom complexes. In 1960, Cody and Williams[5] were the first to define ACS. They reported "a condition with vestibulo-auditory manifestations and ocular findings that include keratitis, uveitis, episcleritis and others but not interstitial keratitis." Twenty years later, Haynes et al.[6] diagnosed ACS "if another significant inflammatory eye lesion in addition to or rather than interstitial keratitis was present." In 1983, Cobo and Haynes[7] suggested that ACS "consists of ocular or orbital inflammatory disease not involving the cornea, but associated with vestibuloauditory disturbance." In contrast to the former authors, Vollertsen et al.[12] do not recognize a separate category of patients with ACS.

At present, most cases exhibiting interstitial keratitis with or without other ocular involvement, which fulfil Cogan's original criteria, are still generally defined as TCS. We think that CS is characterized predominantly by a focal, peripheral interstitial keratitis with typical exacerbations and remissions as originally described by Norton and Cogan.[2] If another significant inflammatory eye lesion in addition to interstitial keratitis is present, we define this complex of symptoms as ACS.

In many CS case reports, the ocular, vestibular, and auditory symptoms do not occur at the same time. The average duration between the onset of eye and ear involvement is 1–2 months.[2,12] Haynes et al.[6] state that the audiovestibular symptoms and the ocular complaints have to occur within 2 years before or after the onset of the disease; otherwise it is not a TCS. Since this is an arbitrary time frame, we do not specify the delay between ear and eye involvement in our definition of the syndrome.

Many patients with CS have unspecific systemic symptoms, such as fever, weight loss, fatigue, headache, arthralgia, myalgia, and abdominal discomfort.

CONCLUSION

We define typical Cogan's syndrome (TCS) as follows:

Bilateral focal, peripheral interstitial keratitis with or without conjunctival hyperaemia or ciliary flush; often with typical exacerbations and remissions; associated with usually bilateral fluctuating sensorineural hearing loss, tinnitus, and

vestibular disturbance; with or without systemic manifestations of unknown origin; without a history of eye or ear disorders preceding the onset of the syndrome.

Our definition of atypical Cogan's syndrome (ACS) is:
The above-described syndrome combined with another significant inflammatory eye lesion in addition to interstitial keratitis.

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CHAPTER 3

HISTOPATHOLOGICAL AND IMMUNOLOGICAL FINDINGS IN COGAN'S SYNDROME

1- Introduction
2- Histopathological findings
3- Immunological findings
4- Discussion and conclusions

1. Introduction

A great number of papers have questioned whether Cogan's syndrome (CS) represents a vasculitis.[1-13] In 1953, Oliner et al.[9] were the first to describe a vasculitis (giant cell angiitis) in typical Cogan's syndrome (TCS). Haynes et al.[7] found seven cases of atypical Cogan's syndrome (ACS) and 1 case of TCS with histopathologically confirmed vasculitis. On the other hand, many authors could not find signs of vasculitis in the biopsies studied.[14,15] Other investigators have suggested that CS is an autoimmune disease.[7,10,16-20]

In this chapter, we will review the histopathological and immunological findings in CS and discuss the suggested vascular and immunological pathogenesis. We will use the definitions of TCS and ACS as formulated in Chapter 2. In some cases,[12] it was impossible to differentiate between ACS and TCS and, therefore, we used the general qualification CS in these cases.

2. Histopathological findings

The histopathological findings in patients with CS are extremely diverse. First of all, CS concerns the eye and audiovestibular organs. Because vasculitis is assumed to play an important role in the pathogenesis of CS and aortic insufficiency is a serious cardiac lesion complicating CS, the histopathological findings in the cardiovascular system will also be discussed here.

2.1. THE EYE

Of the four known pathological case reports, only 1 concerns an ACS;[1] all other patients had TCS. Two autopsy reports[1,14] describe a thickening of the corneal epithelium and newly formed capillaries in the cornea near the limbus. In one of these cases,[14] Bowman's membrane in the left eye was markedly distorted and focally absent, Descemet's membrane was distinctly festooned but intact, and the globe was distorted and atrophic (Table 1).

The angles of the anterior and posterior chambers were completely obliterated. Negroni and Tiberio[21] observed neo-vascularization, without vasculitis in the cornea. Infiltrates of plasma cells, mononuclear leukocytes and lymphocytes were seen in the conjunctiva,[1,14,22] the deep layers of the cornea,[21] and in the adjacent sclera and iris.[1,14] Moderate hyalinization of arterioles around the optic nerve was observed, and the choroid and ciliary body were infiltrated with plasma cells and lymphocytes.[1,14]

Table 1. Histopathology of the eyes.

Site	Pathology	Case reports (N = 4)			
		1 ACS	14 TCS	21 TCS	22 TCS
Cornea:	infiltration deep layer:				
	- plasma cells, lymphocytes			+	
	- mononuclear leukocytes			+	
- epithelium	thickening	+	+		
- Bowman's membrane	distorted		+		
- Descemet's membrane	festooned		+		
- perilimbal	neo-vascularization	+	+	+	
	vasculitis			−	
Conjunctiva, sclera,	infiltration:				
Uvea, and choroid	- plasma cells, lymphocytes	+	+		+
	- mononuclear leukocytes	+	+		+
Optic nerve	hyalinization of arterioles	+	+		

Case: 1 (Bernhardt et al., 1976); 14 (Fisher & Helström, 1961); 21 (Negroni et al., 1969); and 22 (Bischoff, 1972); (+): present; (−): not present.

2.2. THE AUDIOVESTIBULAR ORGANS

To date, five pathological studies of the temporal bone in patients with CS have been published.[14,15,23-25] In two of these,[23,24] the clinical symptoms are not in agreement with the diagnostic criteria as formulated by Cogan[26] and Norton and Cogan.[27]

Wolff et al.[23] described a case with bilateral sensorineural hearing loss, pigment changes in the eyelashes, conjunctivitis, uveitis, exudative retinal detachment, and loss of hair; however, the patient did not exhibit the obligatory keratitis. Therefore, this case might be more typical of the Vogt-Koyanagi-Harada syndrome.
The patient reported by Zechner[24] demonstrated hearing loss in early childhood and did not suffer from keratitis at all.

The three cases reported by Fisher and Hellström,[14] Rarey et al.,[15] and Schuknecht and Nadol[25] showed bilateral interstitial keratitis, total bilateral deafness, and clearly suffered from vertigo with vegetative reactions. These case reports concern ACS in view of the fact that Rarey et al.[15] described an uveitis and episcleritis, and Schuknecht and Nadol[25] observed an episcleritis. In all cases, the middle ear showed no obvious signs of pathology. Fisher and Hellström[14] noticed infiltration of lymphocytes and plasma cells in the spiral ligament of the cochlea. The membranous lining of the cochlea, semicircular canals, utricle, and saccule was hypertrophic. The endolymphatic spaces of the cochlea and the semicircular canals, as well as the perilymphatic spaces of the semicircular canals, contained a dense, acidophilic deposit.[15,25] Rarey et al.[15] reported new bone formation, but no fibrosis. A severe ossification had occurred in both ears within the membranes of the labyrinth. There

was complete ossification of the apical cochlear turns, whereas in the basal turn only the scala tympani was patent. The contents of the modiolus had degenerated and become replaced by bone. Ectopic bone formation was seen in each of the three semicircular canals, but they were not completely obliterated. Schuknecht and Nadol[25] found new bone formation in the scala tympani of the lower basal turns. Endolymphatic hydrops was seen in the scala media, and Reissner's membrane was intact.[14,25] The number of nuclei of all cells in the organ of Corti had diminished.[14,25] Only the Hensen's cells could be identified. The stria vascularis was severely atrophied throughout the entire cochlea.[25] Demyelination and atrophy of the proximal portion of the cochlear nerve were seen,[14,15,25] while the vestibular and spiral ganglia

Table 2. Histopathology of the labyrinth.

Site	Pathology	Case reports:		
		14 TCS	15 ACS	25 ACS
COCHLEA				
- organ of Corti	number of cells diminished	+		+
- spiral ligament	infiltration:			
	- lymphocytes	+		
	- plasma cells	+		
	atrophy			+
- stria vascularis	atrophy			+
- modiolus	osteoneogenesis		+	
- scala tympani	osteoneogenesis		+	+
	fibrosis			+
- scala vestibuli	osteoneogenesis		+	
- scala media	fibrosis			+
	endolymphatic hydrops	+	+	
- membranous lining	hypertrophy	+		
- cochlear nerve	demyelination, atrophy	+	+	+
- spiral ganglion	satellitosis	+		
VESTIBULAR LABYRINTH				
Semicircular canals:				
- membranous lining	hypertrophy	+		+
- perilymphatic space	fibrosis	+		
	osteoneogenesis		+	
Vestibular aquaeducts	fibrosis			+
	osteoneogenesis			+
Utricle/saccule:				
- membranous lining	hypertrophy	+		+
	fibrosis			+
INNER EAR ARTERIES	diminished in number and diameter			+
	vasculitis	–	–	–

Case: 14 (Fisher and Helström, 1961); 15 (Rarey et al., 1986); and 25 (Schuknecht and Nadol, 1994); (+): present; (–): not present.

exhibited satellitosis.[14] The arteries of the inner ear showed a diminished number and a decrease in diameter,[25] but no definite vasculitis was noted in either case (Table 2).

2.3. THE CARDIOVASCULAR SYSTEM

With the exception of infectious angiitis, the causes and pathogenesis of many vasculitic syndromes are either unknown or incompletely understood. Vasculitis may be caused by deposition of immune complexes. For instance, deposition in medium and small arteries causes polyarteritis nodosa, whereas deposition in venules produces angiitis. Establishing the cause of vasculitic syndromes, either by immunological or other techniques, is usually not possible, since there are no causally specific tests.[28] Nevertheless, Lie[28] has formulated a clinical classification of vasculitic syndromes (Table 3).

Aorta: Aortic insufficiency, sometimes associated with aortitis, is the most serious cardiac lesion complicating CS.[4,7,10-13,29-31] Consequently thorough histopathological investigations have been performed.
Vollertsen et al.[12] performed angiography in two patients. They discovered diffuse irregular narrowing of the aorta. In two ACS cases, the aorta and the coronary ostia were found to be narrowed in the region of the aortic valve.[10,31] In another patient, however, Vollertsen et al.[12] found generalized aortic dilatation. The thoracic aorta showed fibrinoid thickening in a patient with ACS,[1] and the lumen of the abdominal aorta was narrowed by either thrombi or thickening of the aortic wall in two typical

Table 3. Clinical classification of vasculitic syndromes (modification by Lie[28])

Infectious angiitis:
- Syphilitic
- Viral
Non-infectious angiitis:
Involving large, medium-sized and small blood vessels
- Arteritis of rheumatic-rheumatoid disease
Involving predominantly medium-sized and small blood vessels
- Thromboangiitis obliterans (Büerger's disease)
- Polyarteritis
- Polyarteritis nodosa
- Pathergic-allergic granulomatosis and angiitis
- Wegener's granulomatosis
- Vasculitis of collagen-vascular disease
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Relapsing polychondritis
- Sjögren's syndrome
- Behçet's syndrome
- Cogan's syndrome

cases.[5,32] Other authors[29] reported a normal abdominal aorta in TCS. Histological examination showed involvement of all layers of the aorta, with predominance of the media and intima in both syndromes.[1,29,32] The major changes were the following: an infiltrate of neutrophils and mononuclear cells; hypertrophy of fibrous tissue; occasional giant cells; disruption of the elastic membrane; neo-vascularization (vasa vasorum); necrosis; and scarring in 1 patient with ACS and two patients with TCS.[1,14,32] The findings may extend into the proximal part of the coronary artery and sinus of Valsalva in both syndromes.[4,29-32] In 1 TCS and 1 ACS patient, a fibrous thickening of the aorta was found similar to those in Takayasu's arteritis.[1,8]

Aortic valve: The aortic valve of a patient examined by Vollertsen et al.[12] was deformed and fibrotic. Other investigators have reported:

1) receding of the left coronary cusps, which were detached from the aortic wall in TCS;[29]
2) aneurysms of the cusps with a thickened, hyperaemic, opaque and overlying endocardium in both syndromes;[1,29-31] and
3) apparently normal aortic valves in TCS.[32]

Histological examination of the aortic valves[4,8,12] has shown:

1) acute and chronic inflammation with neutrophilic, lymphocytic, and histiocytic infiltration;
2) small, fibrotic granulomas; and
3) neo-vascularization.

The inflammation had extended into the aorta. Areas of focal fibrinoid necrosis and fibromyxoid changes with associated proliferation of smooth muscle cells have been evident in 1 ACS and two TCS.[4,29,30] Various patients with CS showed only acellular fibrosis and focal, cellular fibromyxoid changes.[10,12,29]

Other vessels: Because of the possible involvement of vascular lesions in CS, Vollertsen et al.[12] performed angiography in two patients. They found a diffuse, irregular narrowing of the iliac arteries, as well as occlusions and stenosis of iliac, femoral, tibial, mesenteric, and renal arteries. In both patients a biopsy was taken during exploration of a femoral arterial thrombosis, and this confirmed vasculitis. Tortuous arteries were found in two other patients.[4,12] A biopsy of the temporal artery of one of the latter patients was normal. La Raja[8] demonstrated insufficiency of the mesenteric vessels in TCS, eight years after the first complaints. Oliner et al.[9] described several biopsies in 1 patient with TCS. All biopsies revealed multiple abscesses with peri-arteric changes, and one exhibited subcutaneous nodule giant-cell angiitis. The diagnosis of giant-cell angiitis was suggested by these authors, but they could not exclude the possibility of a reaction to a secondary inflammatory process. Three patients presented vasculitis at the site of a thrombosis in the arm or leg.[12] Pinals[10] described an unusual case, showing a remarkable delay between the first complaints of vasculitis and the final diagnosis of ACS. Three years after a muscle

biopsy, which revealed a vasculitis, the patient developed CS with septic arteritis. Six months after CS was diagnosed, he was found to have aortic insufficiency. In another patient with CS, histological examination of a gastric ulcer and enlarged spleen showed vasculitis in the gastric serosa, along with granulomatous inflammation of the spleen with large vessel vasculitis.[33] Other authors have described involvement of both carotid arteries, and an angiitis of the eighth nerve in a patient with ACS.[1]

In a thoroughly investigated TCS case,[32] no vasculitis was observed in the viscera, the muscles, or the skin. In most biopsies and autopsy case reports of TCS and ACS no definite vasculitis is noted.[12,14,15,21,34,35] According to Hughes et al.,[17] systemic vasculitis has been reported in 20% of the cases with ACS, but rarely in TCS.

Heart: Investigations of the heart have reported a "flabby myocardium," recent infarctions,[1,30,32] and left ventricular hypertrophy with dilatation for both syndromes.[1] Fibrotic pericardium and fibrosis of the papillary muscles of the mitral valve were seen in an autopsy of one of the cases presented by Vollertsen et al.[12] Endocardial fibrosis, infiltration by neutrophils and eosinophils[1,30,32] or monocytes[33] may occur in both ACS and TCS. As noted earlier, the coronary ostia may be narrowed. The coronary arteries in two TCS patients[14,30] and the sinus of Valsalva in 1 ACS case[31] demonstrated vasculitis and formation of aneurysms.[14] Intravascular thrombotic narrowing was seen in 1 ACS case.[33] One TCS case report gave no evidence of primary coronary arteritis.[32]

2.4. OTHER ORGANS AND SYSTEMS

Brain: Post-mortem examination showed random deposition of haemosiderin in the subarachnoid space and gliosis of the occipital lobe in 1 TCS patient.[5] Examination of the brain, including the nuclei of the second and eighth cranial nerves, showed normal findings in another TCS patient.[14]

Lung: Pleural adhesions[5] were found in one TCS patient, while lung edema was found in one ACS patient.

Liver: Granulomas of the liver,[12] occasionally accompanied by macroscopically visible nodules, were seen in both TCS and ACS patients.[36] In addition, hepatic inflammation has been reported in two patients with TCS, including minimal findings localized in the periportal region or portal triad[36] as well as focal loss of hepatocytes with non-specific inflammation.[29] This infiltrate was of the mixed cellular type. Bile duct proliferation[5] and fibrosis may ensue in TCS.[5,29,36]

Gastrointestinal system: One patient with TCS had ulcerations throughout the gastrointestinal tract.[5] In another patient, thickened patches scattered over the antimesenteric surface of the small bowel were accompanied by mucosal ulcers.

Histological examination revealed inflammation of the lamina propria and submucosa, extending to the muscular layer. Furthermore, examination showed granulomas and a predominantly neutrophilic and eosinophilic infiltrate, which was accompanied by mononuclear cells and multinucleated giant cells. A massive eosinophilic infiltrate of the lamina propria was noted in the appendix of this TCS patient.[36] The appendix from one ACS patient was normal,[4] as were the omental biopsies from the gastrointestinal tract in two other patients.[12]

Spleen: One author described necrosis and granulomas in the spleen, whereas cultures for multiple organisms yielded no growth.[12] Three cases of splenic infarction, two of which were associated with splenic vasculitis, have been reported in TCS.[5,14,32]

Lymph nodes: In a patient with TCS,[36] one node contained signs of mild granulomatous inflammation and multinucleated giant cells and macrophages. Six patients, of which three had TCS, exhibited non-specific nodal inflammatory hyperplasia.[10,12,30,36,37]

Bone marrow: Bone marrow with an increased number of granulocytes, megakaryocytes, and plasma cells was found in patients with TCS.[5,12,19] Diminished formation of haemoglobin was seen in two patients, and megaloblastoid erythroid maturation and diminished erythropoiesis were found in 1 patient.[12] One young woman with active TCS had diminished iron stores,[9] whereas another patient had increased predominantly reticuloendothelial iron stores.[12]

Kidneys: Gross cortical scarring was noted in the kidney of 1 patient.[12] Infarction of renal tissue occurred in four other patients, of which three had TCS.[1,5,14,32]

Testicles: Of two TCS patients, 1 had vasculitis with testicular arterial scarring, suggestive of "healed vasculitis,"[5] while the other had hyalinized testicular tissue.[14] A testicular biopsy of a third patient was normal.[12]

Muscle: Myositis was found in one,[5] and necrosis and atrophy in two TCS patients.[5,14]

Synovia: The only reported biopsy of synovial tissue in a patient with ACS demonstrated chronic non-specific synovitis.[10]

Skin: Two TCS patients showed trophic ulcers on legs and arms. They exhibited fusiform nodules in the muscles, some of which were hard, some tender,[5] and they showed fibrosis.[30]

3. Immunological findings

In analogy to the histopathology of CS, the immunological findings in CS are also extremely diverse. Although the cause of CS is still obscure, several authors have posed an immunological origin. This is based on the following considerations.

Sedimentation rate: Almost all authors reported an elevation of the sedimentation rate in the acute stage of the syndrome. Of the patients investigated by Vollertsen et al.,[12] 75% had erythrocyte sedimentation rates of more than 20 mm/hour.

Serum proteins: Vollertsen et al.[12] found decreased values for serum albumin (32%), subnormal levels of gammaglobulin and IgG, and elevated levels of alpha-1-globulins and alpha-2-globulins, IgA,[17,38] IgM,[17] fibrinogen,[17] and C-reactive protein. The levels of haptoglobulin and IgE were normal. In other studies, normal values for IgG, IgM and IgA were reported.[39]
Immunofluorescence studies demonstrated the presence of IgG and IgA in the corneal epithelium, and IgG in healthy inner ear tissue in two patients with CS.[40,41] Anti-corneal antibodies were found at the beginning of the disease or during an exacerbation. After therapy with corticosteroids, the corneal antibodies diminished in two patients.[42]
Various authors[17,43-45] were unable to detect cryoglobulins. Vollertsen et al.[12] found traces of cryoglobulins only in 1 out of 6 patients. However, Haynes et al.[7] reported that 23% of patients suffering from CS have cryoglobulinaemia.

Complement: Vollertsen et al.[12] found a decrease in total haemolytic complement in 10% of all patients. They also found a decrease in C3 in 3 out of 14 patients and a diminished C4 component in 2 out of 12 patients. A decrease of both C3 and C4 was seen in 1 patient. Edström and Vahlne,[39] described a decrease in both C3 and C4, but noted that the decrease in C3 was more profound and of longer duration than that of C4. Other studies showed slightly elevated levels of C3 or a slightly elevated CH50 in ACS.[17] Complement components had normal values in most other studies.[2,4,7,10,17,19,38,43,44,46]

T- and B-lymphocytes: Haynes et al.[7] found an increase in T- and B-lymphocytes in the blood of 2 out of 3 patients studied. During the inactive period of the disease, levels of circulating T- and B-lymphocytes remained elevated. Ocular findings included infiltration of lymphocytes and plasma cells into the cornea and conjunctiva.[7,26] Tests for autoantibodies using extracts of corneal tissue were negative in two patients with ACS.[17]

Lymphocyte stimulation in vitro: Stimulation of lymphocytes with eye-specific proteins (S antigen, outer rod segment, and scleroprotein) was described by Peeters et al.[38] In the study conducted by Arnold et al.,[40] a lymphocyte stimulation test with inner ear extract did not indicate cellular immunity in two patients with ACS.

Mitogen-induced proliferation of lymphocytes was normal in all five patients tested.[16,39]

When memory T-lymphocytes are stimulated by the relevant antigen, they start to proliferate and produce cytokines such as Migration Inhibition Factor (MIF). MIF prevents macrophages and other leukocytes from leaving the site of antigenic stimulation. Hughes et al.[17] demonstrated that an inner ear extract could induce blood lymphocyte proliferation and leukocyte migration inhibition in patients with ACS. Edström and Vahlne[39] found evidence of reduced leukocyte migration in the presence of PPD and C. albicans in 1 patient. Char et al.[16] reported that normal allogenic pooled corneal antigens could induce MIF production by blood lymphocytes from four patients with CS.

All *in vitro* immunological tests performed on 13 patients in a study by Haynes et al.[7] were normal.

Anergy: Edström and Vahlne[39] described a patient in an acute stage of TCS. An episode of transient immunological anergy was accompanied in this patient by a decreased number of circulating T- and B-lymphocytes and signs of complement consumption. Other investigators found no evidence of persistent anergy.[7,11,34,36]

Histocompatibility complex (HLA): Immunogenetical analysis in several patients[6,7,10,16,19,47-49] indicated that initial reports of an increased frequency of HLA-B17 in CS may have been erroneous. The error would be due to the small number of patients studied.[48] HLA-B17 occurs in approximately 8% of the patients with CS,[6] and this antigen was present in 3 out of the 4 patients studied by Char.[16]

Other immunological findings: Rheumatoid factor was found to be positive in two patients.[7,50] It was initially negative in 1 patient, but this factor became positive during follow-up (titer elevation unknown).[51] Low titers of antinuclear antibodies were found in 3 out of 18 patients. Anti-DNA antibodies were absent in 5 patients studied, and the LE-cell test was negative in 18 patients.[12] Immunohistochemical analysis of post-mortem obtained tissue demonstrated no immunoglobulin, C3, or fibrinogen deposition in the aortic valve.[4] In another patient, post-mortem biopsies showed varying amounts of fibrin in inflamed arteries, but without immunoglobulin deposition.[14]

4. Discussion and conclusions

In CS, vasculitis has been demonstrated in several organs. All layers of the walls of medium-sized and small arteries and veins may be involved.[5,14] Intimal proliferation and disruption of the internal elastic membrane may be present,[14,30] and intimal thickening and fibrosis may form chronic lesions.[5,14,30] In some cases the perivascular tissue is involved.[5,14,37] Inflammation, necrosis, and fibrous scarring occur.

The infiltrate may consist of neutrophils, mononuclear cells (including plasma cells and eosinophils),[14,37] and giant cells.[9,14] Whenever present, vasculitis in CS is distributed diffusely throughout the body; there is no specific TCS vasculitis found in the various patients studied. In most biopsies and autopsy case reports, no definite vasculitis is noted.[12,14,15,21,34,35]
Aortic insufficiency, often based on inflammation, is the most serious cardiac lesion complicating CS. It may be associated with aortitis.[4,7,12,13,29-31] Aortic insufficiency can appear at any time during the course of CS.[12]
Case reports, in which temporal bones were studied, reveal deposits of fibrous tissue in the cochlea and semicircular canals.[14,25] Furthermore, Rarey et al.,[15] described osteoneogenesis in more advanced inner ear pathology.[25] No vasculitis was noted.[14,15,25] Infiltrates of plasma cells and lymphocytes were seen in the inner ear and the cornea.[1,14] Neo-vascularization was seen in the inner ear and the cornea, without vasculitis.[1,14,21] The epithelium and Bowman's membrane were intact.[1,14]
Other histopathological findings in CS are extremely diverse. Therefore, other causes should not be ruled out.

If the tissue damage in CS were immunologically mediated, an attempt can be made to clarify the mechanism(s) involved according to the hypersensitivity classification of Coombs and Gell.[52] It is most likely that the type of reaction will be the same in the eye and ear. Type III hypersensitivity, the immune-complex-mediated disease, is prone to multiorgan involvement, since immune complexes circulate and may be deposited in unrelated organs. Basement membranes (e.g. in the stria vascularis) are predilection sites.[53] The hypothesis that systemic vasculitis plays an important primary role in the aetiology of all aspects of CS is dubious, especially since the cornea is a-vascular. Type IV, the cell-mediated (delayed-type) hypersensitivity, implies an interstitial keratitis, due to contact between an (auto-)antigen and the immune system. The nerve cells of the inner ear might be a target for autoreactive effector cells.[53] Both Type II, the antibody-dependent cytotoxic hypersensitivity, and Type IV, (T-) cell-mediated hypersensitivity would imply an involvement of the ear and eye, based on shared auto-antigenic cross-reactivity. Both Types II and IV constitute possible hypersensitivity reactions that are operational in CS.
Nevertheless, an autoimmune basis for CS has still not been proven. To fulfil the criteria of an autoimmune disorder, autoantibodies would have to be demonstrated in a majority of cases. Unfortunately, identification of immunoglobulins, immune-complex depositions, cellular infiltrates and relevant auto-antigens in otological and ophthalmological disorders is hampered by the fact that it is impossible to take a biopsy from the inner ear or the cornea of a living patient. Post-mortem investigation of corneal tissue is possible by using cryotome sections. Immunohistopathological investigation of the inner ear, however, involves fixation and decalcification, which may interfere with the antigenic properties of tissue components. Obviously, autoantibodies may be demonstrated in the serum of patients using relevant substrates (auto-antigens). However, this has only been demonstrated by two groups

of investigators, who could prove the presence of antibodies reacting with structures of healthy inner ear tissue[40] and cornea.[40,42]

It is noteworthy that the cornea and the inner ear are two of the very few immunologically isolated sites in the body. Although the inner ear is accessible to the immune system,[54] various authors have presumed a local immune defense system in the endolymphatic sac. The immunoglobulin content of the perilymph is different from that of CSF and serum,[55] and it is possible to produce a local antibody response in the perilymph, which is not expressed in the serum.[56,57] Indeed, it has been suggested that the endolymphatic sac may be the site of a local immune subsystem.[40,58-61] If one assumes that the inner ear has its own immune defense, relatively independent of the general immune system, it may be impossible to find antibodies in the general circulation.

The cornea enjoys considerable immunological isolation as well. This isolation is due to its a-vascularity and the absence of lymphatic drainage. Antigens embedded in the cornea have limited access to lymphoid tissue, while lymphoid infiltration of the cornea is equally difficult.[62] Furthermore, the epithelium is the richest reservoir of antigen, followed by the endothelium. The relatively a-cellular stroma provides a very limited source.[62] Consequently, cellular infiltration might be largely dependent on vascularization of the cornea.[63]

Non-specific peripheral signs of an inflammatory process (elevated erythrocyte sedimentation rate and leukocytosis) and specific immunological findings have been described only in a limited number of patients. Also, these findings were frequently contradictory. In most patients, no abnormalities could be found at all. Demonstration of the presence of T-lymphocytes, macrophages, and plasma cells, as well as demonstration of a response to immunosuppression, may constitute circumstantial evidence for an immunologically mediated disease. However, these findings do not form sufficient proof of autoimmunity.[53] Involvement of both hearing organs and both eyes might suggest an autoimmune pathogenesis, but unilateral sensorineural hearing loss or unilateral interstitial keratitis do not completely rule out an autoimmune origin. Unfortunately, there are no (combinations of) immunological test results specific to CS.

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CHAPTER 4

A RETROSPECTIVE STUDY OF TYPICAL AND ATYPICAL COGAN'S SYNDROME IN WESTERN EUROPE

1- Introduction
2- Patients and methods
3- Results
4- Discussion and conclusions

1. Introduction

Cogan's syndrome (CS) is relatively rare. Since its description by Cogan in 1945, altogether some 187 cases have been published. Of the 121 publications that we have been able to trace in the literature, 106 deal with a case report of one or two patients; 6 publications report 3 or 4 patients, whereas the other 9 papers present small series of patients.

In his first paper, published in 1945, Cogan reported on 4 patients with "non-syphilitic interstitial keratitis associated with vertigo, tinnitus, or hearing loss". In a second article[2] he added another 4 cases. In 1959, Norton and Cogan published a long-term follow-up of these 8 patients and described 7 new cases. In 1960, Cody and Williams presented another 6 patients, while Haynes et al. (1980, 1981) added a series of 13 patients that was discussed again by Cobo et al. (1984). Finally, in 1985 and 1986, McDonald et al. and Vollertsen et al. reported on the same 18 cases (Table 1).

Table 1. Publications reporting small series of patients with Cogan's syndrome (CS).

Author(s)	Year of publication	Number of cases
1. Cogan	1945	4
2. Cogan	1949	4
3. Norton and Cogan	1959	7
4. Cody and Williams	1960	6
5. Haynes et al.	1980	13
6. Haynes et al.	1981	(same as 5.)
7. Cobo et al.	1984	(same as 5.)
8. McDonald et al.	1985	18
9. Vollertsen et al.	1986	(same as 8.)
Total		52

2. Patients and methods

2.1. PATIENTS

In this study, the findings in 98 patients with the presumed diagnosis of CS are reported and analysed. These patients were treated in Western Europe between 1968 and 1993. The data were derived from two different sources:

1. unpublished cases (N = 76); and
2. published cases (N = 27).

1. Unpublished cases

In 1989, the heads of the ORL departments of 82 university clinics and 485 major hospitals in 13 West European countries were asked whether they had treated

patients with CS. Upon this request they were able to trace the records of 113 patients with the presumed diagnosis of CS. The majority of these departments were subsequently visited and with the help of one of the local colleagues, the data were recorded in a data file (see Addendum). Some colleagues were so kind as to fill out this data file themselves. In all, the data on 76 cases could be collected (Table 2).

Table 2. Number of cases submitted and patients enrolled.

	Cases submitted	Patients enrolled
Departments	113	76
Published reports	27	22
Total number of patients	140	98

2. Published cases

Meanwhile, 48 authors[10-61] from Western Europe, who had reported on CS in the period 1958–1993, were asked to provide us with complete data on the 59 patients they had previously studied. We visited some of them and filled out the data file together. Others were so kind as to complete the file themselves. Data on 22 cases[10-29] could be collected (Table 2).

We could not obtain data on the remaining 32 published and 37 unpublished cases, either because these cases had been examined many years ago and the patient's data had not been kept, or the costs for a personal visit to collect data was considered too high.

2.2. COUNTRIES OF ORIGIN OF THE PATIENTS

The 140 cases that had been submitted originated from 13 countries, while the 98 patients that could finally be enrolled came from 10 different countries (Table 3). The authors who kindly provided us with data on CS patients are listed at the end of this Chapter.

2.3. METHODS

Data file

All data on the cases submitted were collected in a data file (cf., Addendum). For each patient, detailed information about their general medical history, ophthalmological and audiovestibular history, treatment and follow-up was recorded. In most cases ophthalmological, otorhinolaryngological, and other examinations were included.
Data of audiometry and vestibular function tests were collected. Results of general laboratory tests, spinal fluid examinations, immunological and allergological investigations, as well as microbiological and viral examinations were filed. The

Table 3. Number of cases submitted by country and number of patients enrolled in this study.

Country	Cases submitted	Patients enrolled
Austria	2	0
Belgium	5	5
Denmark	3	0
Germany	30	27
Great Britain	17	3
Finland	5	5
France	14	13
Italy	8	3
Netherlands	16	16
Norway	3	3
Spain	3	0
Sweden	19	8
Switzerland	15	15
Total	140	98

findings of radiological, pathological and special examinations such as EEG, EMG and ECG were stored.
In recording all laboratory data, the normal local values were used.

Definition of syndromes

- Typical Cogan's syndrome (TCS): bilateral focal, peripheral interstitial keratitis with or without conjunctival hyperaemia or ciliary flush; often with typical exacerbations and remissions; associated with usually bilateral fluctuating sensorineural hearing loss, tinnitus, and vestibular disturbance; with or without systemic manifestations of unknown origin; and without a history of eye or ear disorders preceding the onset of the syndrome.
- Atypical Cogan's syndrome (ACS): the above-described syndrome, combined with another inflammatory eye lesion in addition to interstitial keratitis.

In some cases it was impossible to differentiate between ACS and TCS; therefore, the neutral qualification CS was used in these cases.

Definitions of terminology

- Initial phase: phase of the syndrome before therapy.
- Average duration of the syndrome: period from initial symptoms until the stationary phase, including exacerbations and remissions of later date.
- Stationary phase: phase of the syndrome when the patient has recovered from his systemic and eye complaints and has stable hearing loss without fluctuations.
- Blindness: permanent visual acuity of less than 20/200.
- Hearing improvement/decrease: change in AC threshold $\geq$ 10 dB.
- Deafness: hearing loss of more than 120 dB for all frequencies.

Statistical analysis

To determine the correlation of clinical features between TCS and ACS, the chi-square test was used. Statistical significance was defined as $p \leq 0.05$.

3. Results

3.1. SYNDROMAL DIAGNOSIS

Of the 98 CS cases enrolled in this study, 39 could not be accepted as suffering from TCS or ACS. Either those patients did not suffer from interstitial keratitis (N = 18), or essential data were not available to ensure a correct diagnosis (N = 21). Of the remaining 59 patients, 37 were classified as suffering from TCS, 22 from ACS (Table 4).

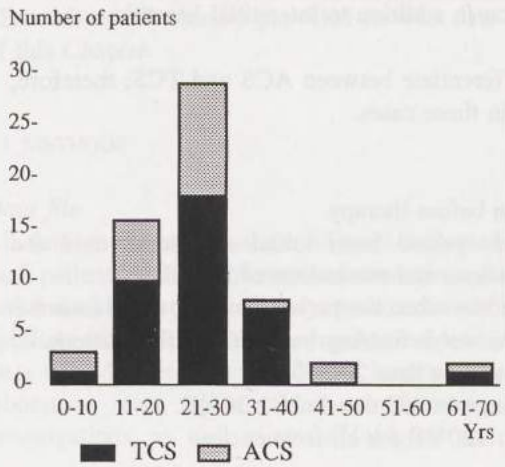
Table 4. Syndromal diagnosis.

Differentiation	Number of patients
Typical Cogan's syndrome (TCS)	37
Atypical Cogan's syndrome (ACS)	22
Non-Cogan's syndrome	39
Total	98

3.2. AGE AND SEX DISTRIBUTION

The average age of onset of TCS was 25 years (range: 10–62) For ACS the average age was 23 years (range: 6.5–44). The syndrome developed between 18 and 35 years of age in 90% of the TCS and 73% of the ACS cases (Fig. 1).

Fig. 1 Average age of onset in TCS and ACS.



The sex distribution was equal in TCS (m:f = 18:19). In ACS a statistically non-significant difference between both sexes was found (m:f = 9:13; chi-square value: 0.73, with one degree of freedom, $p \approx 0.4$; Table 5).

Table 5. Sex distribution in TCS and ACS.

	Male	Female	Total
Typical (TCS)	19	18	37
Atypical (ACS)	9	13	22
Total	28	31	59

3.3. SYMPTOMS AT ONSET

Eye involvement was the first symptom to appear in 37% of the TCS and 45% of the ACS patients. Initial involvement of the audiovestibular system was seen in 26% of the TCS and 32% of the ACS patients. In 26% of the TCS and 18% of the ACS patients both organs (eyes and audiovestibular system) were affected. In 11% of the TCS and 5% of the ACS patients other systems were involved before these patients complained about their eyes or ears (Table 6).

Table 6. First symptom in TCS and ACS.

First symptom	TCS N = 37	ACS N = 22
Involvement of:		
eyes	14 (37%)	10 (45%)
audiovestibular system (AVS)	10 (26%)	7 (32%)
both eyes and AVS	9 (26%)	4 (18%)
other systems	4 (11%)	1 (5%)

The average time lapse between the onset of the ocular and audiovestibular involvement was 1.5 months in TCS and 1 month in ACS. The greatest interval amounted to 11 months in 1 patient with TCS and 2.5 years in 1 patient with ACS.

Ophthalmological symptoms

In 32 TCS cases, and in 15 ACS cases both eyes were involved simultaneously. Less commonly in 4 TCS and in 6 ACS patients, the eye symptoms started unilaterally. In these cases the other eye became involved after a mean interval of 4 weeks. In one TCS and one ACS patient, only the right eye was affected (Table 7).

Table 7. Initial eye involvement in TCS and ACS.

	TCS N = 37	ACS N = 22
Bilateral	32 (86%)	15 (68%)
Unilateral, later bilateral	4 (11%)	6 (27%)
Unilateral	1 (3%)	1 (5%)

Audiovestibular symptoms

All 59 patients suffered from bilateral hearing loss, except for 1 ACS case, who had hearing loss at his right ear only. In 46% of the TCS and 36% of the ACS cases, hearing loss occurred at the same time in both ears. In 30% of the TCS and 41% of the ACS patients it started unilaterally; after an average interval of 2 weeks the other ear was also involved (Table 8).

Table 8. Initial audiovestibular involvement in TCS and ACS.

	TCS N = 37	ACS N = 22
Bilateral	17 (46%)	8 (36%)
Unilateral, later bilateral	11 (30%)	9 (41%)
Unilateral	0	1 (5%)
Unknown	9 (24%)	4 (18%)

In 20 TCS and 7 ACS patients the audiovestibular symptoms started with vertigo. After an average period of 2.5 and 5.2 days, respectively, hearing loss was observed too. In 4 TCS and 2 ACS patients it took 1 to 1.5 months before hearing loss was observed. In 6 TCS and 8 ACS patients, vertigo and hearing loss occurred simultaneously, in 11 and 7 patients, respectively, their sequence was not recorded (Table 9).

Table 9. First audiovestibular symptom in TCS and ACS.

	TCS N = 37	ACS N = 22
Vertigo	20 (54%)	7 (32%)
Vertigo and hearing loss	6 (16%)	8 (36%)
Hearing loss	0	0
Unknown	11 (30%)	7 (32%)

3.4. PRODROMAL DISEASES

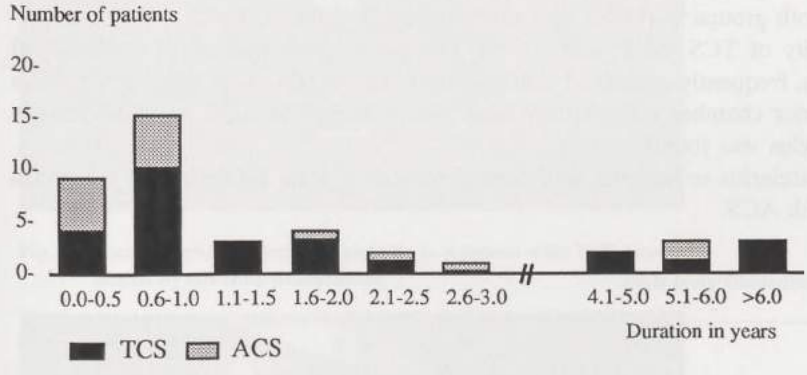
In 16 TCS patients (43%), upper respiratory tract infections preceded the onset of the syndrome (in 15 patients <1 week, and in 1 patient 2 weeks, before the first symptoms). In ACS patients, only 6 (27%) suffered from preceding upper respiratory

tract infection (no statistical difference between TCS and ACS; the Yates-corrected chi-square value was 0.90, with one degree of freedom, $p \approx 0.3$). One TCS patient suffered from chronic sinusitis. None of the patients had undergone active immunization in the year before the first symptoms. Three TCS patients were pregnant at the time of the first symptoms.

3.5. DURATION

The average duration of TCS was 21 months and of ACS 16 months (Fig. 2). Seven TCS and 2 ACS patients had not reached a stationary phase, and in 3 TCS and 4 ACS cases, insufficient data were available.

Fig. 2 Median duration of TCS and ACS.



3.6. OPHTHALMOLOGICAL FINDINGS

Symptoms

In most patients, both eyes were involved, except in one TCS and one ACS patient, who had complaints of the right eye only. Redness, eye discomfort, and photophobia were common findings in both groups (Table 10).

Exacerbations and remissions were seen more often in TCS than in ACS cases (62% and 36%, respectively; chi-square value 6.24; $P \approx 0.01$). Unfortunately, we do not know whether, in the remaining TCS and ACS patients exacerbations and remissions were present.

In 8 TCS and 7 ACS patients, visual acuity was disturbed bilaterally. One patient with TCS complained of diplopia.

Signs

Interstial keratitis was by definition present in all patients (Figs. 3–4). In a majority it was found bilaterally. In only 2 TCS and 1 ACS patient keratitis was unilateral.

Table 10. Ophthalmological symptoms.

	TCS (N = 73 eyes)	ACS (N = 43 eyes)
Redness	52 (71%)	37 (86%)
Eye discomfort	50 (69%)	34 (79%)
Photophobia	44 (60%)	25 (58%)
Exacerbations and remissions	46 (63%)	16 (37%)
Disturbance of visual acuity	16 (22%)	14 (33%)
Diplopia	2 (3%)	0

In 44% of the TCS and 54% of the ACS patients, focal peripheral opacities were described precisely, whereas in 56% and 46% of the cases opacities were found, but their localization and appearance were not described (Table 11).
Episcleral and perilimbal injections of the cornea without deep vascularization were found in both groups at almost the same percentage (Figs. 3-5).
The majority of TCS (62%) and ACS (72%) patients complained of conjunctival hyperaemia, frequently combined with excessive lacrimation (37%, resp. 56%). Cells in the anterior chamber and a ciliary flush were common in ACS. In all patients, a normal fundus was found.
Uveitis, episcleritis or scleritis, and corneal ulceration were by definition present in patients with ACS.

Table 11. Ophthalmological signs.

	TCS (N = 73 eyes)	ACS (N = 43 eyes)
Interstitial keratitis	72 (99%)	43 (100%)
Opacity near the limbus	32 (44%)	24 (54%)
Diffuse episcleral injection	19 (26%)	13 (30%)
Hyperaemic perilimbal vessels	18 (25%)	13 (30%)
Deep corneal vascularization	0	0
Conjunctival hyperaemia	45 (62%)	31 (72%)
Excessive lacrimation	27 (37%)	24 (56%)
Cells anterior chamber	9 (12%)	14 (33%)
Ciliary flush	6 (8%)	8 (19%)
Uveitis	0	35 (81%)
Episcleritis	0	13 (30%)
Scleritis	0	8 (19%)
Thinned sclera	0	4 (9%)
Corneal ulceration	0	4 (9%)
Glaucoma secondary	0	1 (2%)
Blindness	1 (1%)	0

Fig. 3 Interstitial keratitis and conjunctival hyperaemia in a patient with TCS. Note the midstromal corneal opacity (arrow).

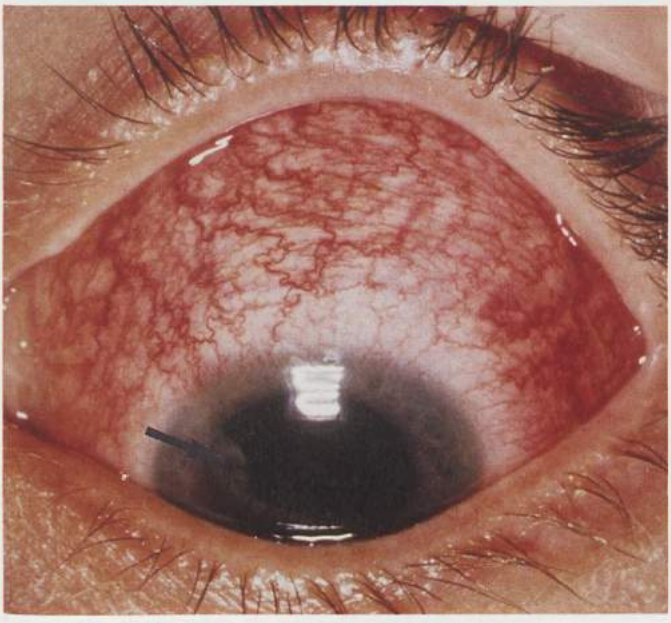


Fig. 4 Focal peripheral interstitial keratitis in a patient with TCS demonstrated by slit-lamp examination.

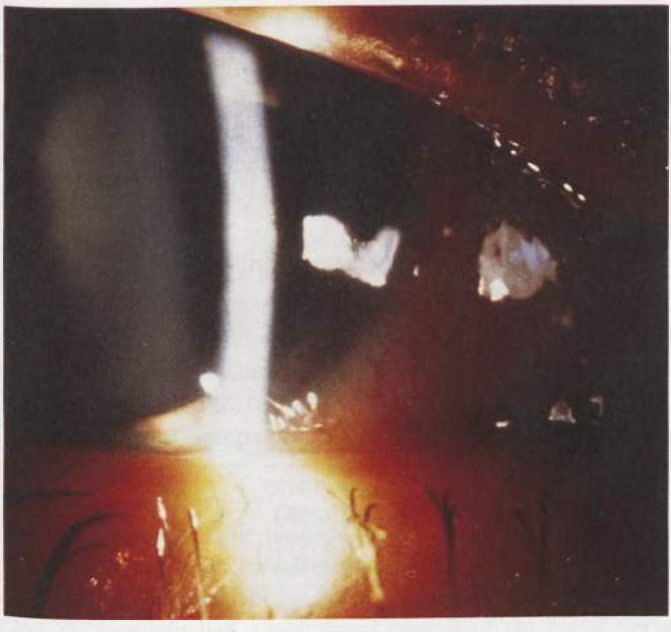
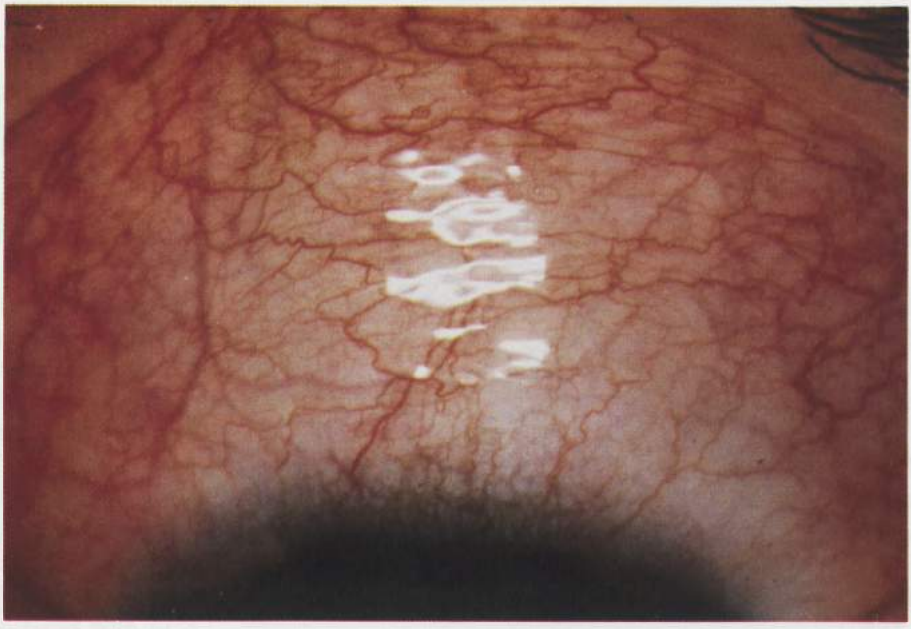


Fig. 5 Close-up view of perilimbal hyperaemia in TCS.



3.7. AUDIOVESTIBULAR FINDINGS

Auditory symptoms

All 59 patients showed bilateral sensorineural hearing loss, with the exception of 1 ACS case, who had a unilateral hearing loss. Tinnitus was a frequent symptom in both groups (84% and 86%, respectively). One-third of the patients mentioned fullness in the ears (32% and 33%, respectively). All patients, except those who became deaf immediately, complained of exacerbations and remissions of hearing, especially at the lower frequencies (Table 12).

Total deafness occurred in TCS in 27% of the patients (7 bilateral and 6 unilateral) and in 19% (3 bilateral and 2 unilateral) of the ACS cases.

Table 12. Auditory symptoms.

	TCS (N = 74 ears)	ACS (N = 43 ears)
Sensorineural hearing loss	74 (100%)	43 (100%)
Fluctuations in hearing	68 (92%)	41 (95%)
Tinnitus	62 (84%)	37 (86%)
Fullness in the ears	24 (32%)	14 (33%)

Vestibular symptoms

Vertigo was nearly always present and usually accompanied by vegetative reactions such as nausea and vomiting. In both groups, 32% of the patients complained of ataxia (Table 13).

Table 13. Vestibular symptoms and signs.

	TCS (N = 37)	ACS (N = 22)
Symptoms		
vertigo	33 (89%)	21 (95%)
vegetative reactions	30 (81%)	18 (82%)
dysbalance	4 (11%)	0
Signs		
ataxia	12 (32%)	7 (32%)

3.8. SYSTEMIC FINDINGS

Complaints

One-quarter of the patients in both groups had complaints of fever, loss of weight and fatigue during the disease. One-third complained of headache (Table 14). Except for ataxia, there were no neurological symptoms.

Musculoskeletal complaints were seen both in ACS and in TCS (41% versus 16%, with a mere suggestion of statistical significance, chi-square value 3.23, $p<0.10$). Three TCS patients complained of arthralgia of unknown origin for 17, 12 and 3 years, respectively, before the onset of CS.

Vague abdominal discomfort was seen in both groups, without statistical significant difference (16% versus 23%, chi-square value 0.08, $p \approx 0.8$). In 2 patients, (1 TCS and 1 ACS), a loud systolic murmur was heard on abdominal auscultation. One TCS patient underwent an appendectomy. A gastrojejunostomy was performed in 1 ACS patient because of a functional duodenal stenosis during the disease.

Three males from the TCS group complained about testicular pain.

In 1 ACS patient aortic insufficiency was found and in another mitralis insufficiency. In none of the patients vasculitis was described.

One ACS patient developed Eale's disease (a retinal vasculitis) 2 years after the first symptoms of CS, presumably caused by treatment with prednison. Two TCS patients had a trombophlebitis of the legs.

Three patients developed psychological problems, i.e. depression.

Past medical history

In some patients, their medical history may have been of importance. One ACS patient suffered from juvenile rheumatoid arthritis, 18 years before the onset of CS. Another ACS patient showed X-ray changes suggestive of ankylosing spondylitis. One TCS patient had a peripheral paresis of the facial nerve 3 months before the

Table 14. Main systemic findings.

	TCS (N = 37)	ACS (N = 22)
NON-SPECIFIC		
Fever	8 (22%)	6 (27%)
Weight loss	6 (16%)	2 (9%)
Fatigue	8 (22%)	7 (32%)
HEAD AND NECK		
Headache	13 (35%)	8 (36%)
Poorly localized discomfort	1 (3%)	3 (14%)
Temporal pain	4 (11%)	3 (14%)
Periorbital pain	1 (3%)	5 (23%)
Posterior auricular pain	2 (5%)	2 (9%)
NEUROLOGICAL		
Central nerve involvement	0	0
Peripheral nerve involvement	0	0
Ataxia	12 (32%)	7 (32%)
MUSCULO-SKELETAL		
Arthralgia and myalgia	6 (16%)	9 (41%)
Arthritis	3 (8%)	3 (14%)
ABDOMINAL		
Discomfort	6 (16%)	5 (23%)
Haemorrhage	0	0
CHEST		
Dyspnea/cough	3 (8%)	3 (14%)
Pleuritis	0	0
Mild, transient roentgenographic abnormalities	0	0
GENITO-URINARY		
Testicular pain	3 (8%)	0
CARDIOVASCULAR		
Dyspnea	0	0
Systolic murmur	1 (3%)	2 (9%)
Aortic insufficiency	0	1 (5%)
Mitralis insufficiency	0	1 (5%)
Vasculitis	0	0
CUTANEOUS		
Nodules	1 (3%)	0
Non-specific rash	1 (3%)	0
LYMPHORETICULAR		
Lymphadenopathy	0	0
Splenomegaly	0	0
Hepatomegaly	0	0
PSYCHOLOGICAL		
Depression	2 (5%)	1 (5%)
Stress	4 (11%)	0

first symptoms, another patient developed a peripheral facial nerve paresis during the second week of ACS. In both patients the paresis healed completely.
In 1 TCS patient the hearing loss started 1 week after a car accident.
One TCS patient was known to have hypertension and a dilated left ventricle, and one ACS patient was known to have angina pectoris.
One ACS patient developed colitis ulcerosa 3 years before the initial symptoms of CS.
One female was born with Turner's syndrome and developed TCS syndrome when she was 19 years of age.

3.9. GENERAL LABORATORY FINDINGS

General findings

An elevated erythrocyte sedimentation rate was found in 78% of the TCS and 86% of the ACS patients. Leukocytosis was observed in 44% of the TCS and 64% of the ACS patients. Slight eosinophilia (5% and 7%) was seen in 2 patients of the atypical group (Table 15). There was no thrombocytosis, and only 1 TCS patient demonstrated a normochromic-normocytic anaemia.

Table 15. General laboratory findings.

	TCS (N = 37)			ACS (N = 22)		
	Increased	Normal	Decreased	Increased	Normal	Decreased
ESR	29 (78%)	8 (22%)		19 (86%)	3 (14%)	
WBC	16 (44%)	21 (56%)		14 (64%)	8 (36%)	
Haemoglobin		37 (100%)			22 (100%)	
Electrolytes		37 (100%)			22 (100%)	

All patients had a normal liver function, except for one TCS patient with a cholecystatic liver disorder (found on biopsy). Kidney function and urine analysis were normal in both groups. Thyroid function tests were normal as well (Table 16).

Table 16. General laboratory findings. Number of patients with increased, normal, or decreased organ function compared to total number of patients examined.

	TCS			ACS		
	Increased	Normal	Decreased	Increased	Normal	Decreased
Liver		36/37			22/22	
Kidney		37/37			22/22	
Thyroid		9/9			9/9	

Serum proteins

The levels of a number of serum proteins were increased in several patients of both groups. Especially alpha-2-macroglobulin was increased (TCS 9/20 and ACS 7/18). In a few patients the levels of alpha-1-macroglobulin and beta-globulin were elevated. In 1 TCS patient, the thyreoglobulin level was elevated with normal thyroid function. Increased values of C-reactive protein were found in both groups. Cryoglobulins were not present in 2 TCS and 5 ACS patients (Table 17).

Table 17. Serum protein findings. Number of patients with increased, normal, or decreased serum protein values compared to total number of patients examined.

	TCS			ACS		
	Increased	Normal	Decreased	Increased	Normal	Decreased
Albumin		22/22			18/18	
Alpha-1-globulin	3/20	17/20		1/18	17/18	
Alpha-2-globulin	9/20	11/20		7/18	11/18	
Beta-globulin	1/20	19/20		1/18	17/18	
Gamma-globulin		20/20			17/17	
Thyreoglobulin		1/20				
C-reactive protein	9/12	3/12		5/ 6	1/ 6	
Fibrinogen	2/ 8	6/ 8		2/ 8	6/ 8	
Cryoglobulins		2/ 2			5/ 5	

3.10. IMMUNOLOGICAL FINDINGS

Complement

C3, C4,and C1q were increased in a few patients only. In 1 ACS patient C3 was decreased (Table 18).

Table 18. Serum complement. Number of patients with increased, normal , or decreased complement values compared to total number of patients examined.

	TCS			ACS		
	Increased	Normal	Decreased	Increased	Normal	Decreased
C3	2/18	16/18		1/14	12/14	1/14
C4	1/18	17/18		1/14	13/14	
C1q	2/18	16/18		2/14	12/14	
CH50	1/3	2/ 3				

Immunoglobulins

IgA, IgM and IgG were elevated in a few patients only. IgE was not examined (Table 19).

Table 19. Serum immunoglobulins. Number of patients with increased, normal, or decreased immunoglobulin values compared to total number of patients examined.

	TCS			ACS		
	Increased	Normal	Decreased	Increased	Normal	Decreased
IgA	1/19	18/19		-	-	
IgM	2/19	17/19		2/12	10/12	
IgG	3/19	6/19		3/12	9/12	

Table 20. Serum antibodies. Number of patients in wich antibodies were found (positive) or not found (negative) compared to total number of patients examined.

Antibodies	TCS		ACS	
	Positive	Negative	Positive	Negative
Rheumatoid factor				
Rose-Waaler test	1/18	17/18		11/11
Latex fixation test	1/7	6/7		6/6
LE-cell test	1/4	3/4		6/6
ACE		4/4		4/4
ANCA		4/4		4/4
Coombs		7/7		5/5
		5/5		1/1
Anti-cornea	1/1	-	3/3	-
Anti-inner ear		-	2/2	
Anti-thyroid		8/8		8/8
Anti-smooth muscle		9/9		
Anti-striated muscle		5/5		
Anti-pancreas				1/1
ANA		21/21		14/14
ENA		10/10		7/7
Anti-DNA		2/2		4/4
Anti-RNA		1/1		-
Anti-microsomal		1/1		
Anti-mitochondrial		7/7		
Anti-parietal cell		7/7		
Anti-cardiolipin				1/1
Anti-glomerular membrane				2/2
Anti-endoplasmic reticulum				1/1
Anti-*Streptococcus*		9/9		5/5
Anti-*Staphylococcus*		3/3		-
Circulating complexes		6/6		4/4

ACE: angiotensin-converting enzyme; ANCA: antineutrophil cytoplasmic antibody; ANA: anti-nuclear antibody; ENA: antibodies to extractable nuclear antigens.

Antibodies
Of all antibody tests carried out, rheumatoid factor was found to be increased in only 1 TCS patient. The Rose-Waaler and Latex fixation tests were increased in another TCS patient (Table 20).

Immunofluorescence studies demonstrated IgG and IgA in the corneal epithelium of 1/1 TCS and 3/3 ACS patients. Corneal antibodies were found in 1/1 TCS at the beginning and during an exacerbation. After therapy with corticosteroids, the corneal antibodies diminished in 2 patients (1/1 TCS and 1/1 ACS; see Chapter 6). Antibodies to inner ear tissues (stria vascularis, spiral ligament, and vestibular dark cells) were found by means of indirect immunofluorescence in 2 ACS patients.

Lymphocyte stimulation in vitro
Stimulation of lymphocytes with eye-specific proteins (S antigen, outer rod segment, or scleroprotein) was observed in 1 ACS patient. In 2 other ACS patients a blood lymphocyte stimulation test with inner ear extract did not give any indication of cellular immunity.

In 1 TCS patient, IgM, IgG, C3, C4 and C1q were extremely elevated. The erythrocyte sedimentation rate was 65 mm/h, and this patient had leukocytosis and elevated titers of herpes simplex. Clinically, no herpes infection or inflammation was seen.
In another patient, demonstrating the acute stage of ACS, an episode of transient immunological anergy was accompanied by a decreased number of circulating T- and B-lymphocytes and signs of complement consumption.

3.11. MICROBIOLOGICAL FINDINGS

Bacteriological findings
Serological tests for syphilis were performed in 37 TCS and 22 ACS patients and all proved negative. Except for 1 TCS case with appendicitis no bacterial infection was present (Table 21).
In 6 TCS and 4 ACS cases, investigations failed to reveal evidence of previous infection by *Borrelia burgdorferi.*
Serological as well as conjunctival cultures for *Chlamydia trachomatis* were negative in both groups (2 and 8 patients). In 1 case, *Chlamydia psittaci* was isolated from the conjunctiva, and titers of type-specific serum anti-Chlamydial antibodies were elevated. The patient died and autopsy was carried out. Unfortunately, no tissue samples were taken from the eyes and ears and no material was obtained for detection of *Chlamydia psittaci* from the various cardiac and other lesions, so the aetiology of the otological, cardiovascular, and ocular lesions is not certain.
Mantoux tests were negative in 5/5 TCS and 5/5 ACS patients.

Table 21. Microbiological findings. Number of patients in who cultures or serological research were positive or negative compared to total number of patients examined.

	TCS		ACS	
	Positive	Negative	Positive	Negative
BACTERIA				
Spirochaeta:				
Treponema pallidum		37/37		22/22
Leptospirosa		3/ 3		2/ 2
Borrelia burgdorferii		6/ 6		4/ 4
Enterobacteriaceae:				
Salmonella typhi		4/ 4		1/ 1
S. paratyphi		3/ 3		-
S. typhimurium		1/ 1		-
Shigella		1/ 1		-
Yersinia		3/ 3		2/ 2
Pseudomonacae:				
Brucella (abortus, melitensis)		6/ 6		6/ 6
Bordetella pertussis		-		1/ 1
Listeria monocytogenes		3/ 3		-
CHLAMYDIA:				
Chlamydia trachomatis		2/ 2		8/ 8
Chlamydia psittaci		2/ 2		-
Rickettsiae (Burnetti, Q-fever)		4/ 4		3/ 3
Mycoplasma		6/ 6		6/ 6
PROTOZOA:				
Malaria		2/ 2		-
Leishmania		1/ 1		-
Entamoeba histolytica		1/ 1		-
Toxoplasma		7/ 7		9/ 9
FUNGI:				
Candida albicans		1/ 1		1/ 1

Virological findings

In 2/14 patients an elevated titer of herpes simplex was found (Table 22). In both patients, we could not find an active infection. A few patients had an elevated titer for influenza type A or B, or parainfluenza virus.

Table 22. Virological findings. Number of patients who exhibited signs and symptoms of acute viral infection. Elevated (positive) or not elevated virus titer (negative) compared to total number of patients examined.

	TCS		ACS	
	Positive	Negative	Positive	Negative
Herpesviridae:				
Herpes simplex virus	2/14	12/14		10/10
Varicella-zoster virus		12/12		7/ 7
Cytomegalovirus		11/11		10/10
Epstein-Barr virus		6/ 6		8/ 8
Orthomyxoviridae:				
Influenza A virus		10/10	1/5	4/ 5
Influenza B virus		10/10	2/7	5/ 7
Paramyxoviridae:				
Parainfluenza virus		9/ 9	1/3	2/ 3
Measles virus		9/ 9		4/ 4
Mumps virus		9/ 9		7/ 7
Respiratory syncytial virus		4/ 4		5/ 5
Enteroviridae:				
Enterovirus		2/ 2		1/ 1
Echovirus		5/ 5		3/ 3
Coxsackievirus (A/B)	1/11	10/11		5/ 5
Poliovirus		4/ 4		4/ 4
Hepatitis A virus		5/ 5		1/ 1
Rotavirus		1/ 1		-
Corona virus	1/ 1	-		-
Adenovirus		7/ 7		9/ 9
Rubella (German measles)		7/ 7		5/ 5
Hepatitis B virus		8/ 8		5/ 5
Human immunodeficiency virus		3/ 3		2/ 2

3.12. OTHER EXAMINATIONS

CSF

Complete screening of cerebrospinal fluid was normal in all 19 TCS and all 13 ACS patients tested.

Allergy

One ACS patient was known to have hay fever. Another TCS patient had a house dust allergy.

Echography

Echo of the abdomen in 5 patients with CS showed no aberrations. Echocardiography was normal in 2 TCS and 4 ACS patients. In 2 ACS patients with aorta and mitralis insufficiency, this investigation was not performed, but electrocardiography showed signs of left ventricular enlargement in those cases.

Plain X-ray studies
On conventional radiographical examination, no abnormalities were observed (Table 23).

Table 23. Plain radiographs.

	TCS normal	ACS normal
Temporal bone	19/19	9/ 9
Sinus	12/12	6/ 6
Thorax	21/21	12/12
Abdomen	2/ 2	-

Computed tomography (CT) and magnetic resonance imaging (MRI)
CT-scanning of the temporal bones was carried out in 25/25 TCS and 13/13 ACS patients. No abnormalities were observed.
In a combined CT and MRI study of 2 TCS and 3 ACS patients, no pathology was seen in 1 patient, who recovered completely. Narrowing or obliteration with soft tissue of parts of the vestibular labyrinth was seen in the remaining 4 patients and in 3 patients, we found aberrations in the cochlea consistent with the audiological data. In only 1 ACS patient calcifications of the basal turn of both cochleas were seen and, using Gadolinium, contrast-enhancement of the cochlea and vestibular labyrinth was seen in another case, probably caused by obstructive vasculitis. For more details the reader is referred to Chapter 8. CT-scans of the cerebrum, abdomen and thorax revealed no abnormalities.

Other scans
Angiography (1 TCS and 1 ACS) revealed no abnormalities. Radionuclear examination, leukocyte and technetium scans showed no signs of abscess or osteomyelitis (2 TCS and 1 ACS).

3.13. HISTOPATHOLOGICAL FINDINGS

Biopsies of skin, fascia and muscle were normal and revealed no vasculitis. Abnormalities were found in 5 ACS patients only. In 1 patient non-specific vascular changes were found in the skin. In another patient, aspecific inflammatory changes were found in a lymph node. Biopsy specimens of the bowel showed a non-specific colitis in one and a biopsy specimen of the stomach of another patient revealed increased numbers of granulocytes and giant cells, with a tendency to abscess formation. Bone marrow examination revealed an increased number of lymphocytes in 1 patient (Table 24).

Table 24. Histopathological findings. Number of patients in which histopathological changes were found compared to total number of patients examined.

Biopsy	**TCS** (N = 37) normal	abnormal	**ACS** (N = 22) normal	abnormal
Skin	5/5		4/5	1/5: non-specific perivascular changes
Fascia	5/5		5/5	
Muscle	5/5		5/5	
Lymph node	-		2/3	1/3: aspecific inflammatory changes
Stomach	-		-	1/1: granulocytes, giant cells and tendency to abscess
Bowel	1/1		-	1/1: non-specific colitis
Bone marrow	2/2		-	1/1: increased number of lyphocytes

3.14. EFFECTS OF GLUCOCORTICOID TREATMENT

Effect on ophthalmological symptoms in TCS

Of the 37 patients 33 were treated by systemically and topically administered glucocorticoids, 1 by systemic glucocorticoids only, while 3 patients received local glucocorticoids only.

In all patients the ophthalmological symptoms and signs were cured irrespective of the therapy and treatment delay (Table 25).

Table 25. Duration of glucocorticoid therapy in 37 TCS patients until the ophthalmological symptoms were cured.

	Improvement of opthalmological symptoms in relation to duration of treatment				
Duration / Treatment	≤ 1 week	1-2 weeks	> 2 weeks	Unknown duration	Total
Systemic & topical	4	10	7	12	33
Systemic	1	-	-	-	1
Topical	1	1	1	-	3
Total	6	11	8	12	37

In 17 cases amelioration was seen within 2 weeks. For 12 patients no information was available about the duration of the therapy until improvement occurred. The 3 patients treated with topical glucocorticoids only recovered within 1-3 weeks.

Effect on ophthalmological symptoms in ACS

Of the 22 patients 18 were treated with systemic and topical glucocorticoids, while 4 patients received local glucocorticoids only. As in TCS, all ophthalmological symptoms and signs were cured irrespective of the therapy and treatment delay (Table 26).

Table 26. Duration of glucocorticoid therapy in 22 ACS patients until the ophthalmological symptoms were cured.

	Improvement of opthalmological symptoms in relation to duration of treatment				
Duration / Treatment	≤ 1 week	1-2 weeks	> 2 weeks	Unknown duration	Total
Systemic & topical	1	4	9	4	18
Systemic	-	-	-	-	-
Topical	-	2	2	-	4
Total	1	6	11	4	22

In 7 cases amelioration was seen within two weeks. The 4 patients treated with topical glucocorticoids recovered in 1-3 weeks. In 4 cases no information was available about the duration of the therapy until improvement occurred.

Effect on auditory symptoms in TCS

Of 37 patients 34 were treated with systemic glucocorticoids. In only 9 (27%) permanent improvement of hearing was seen (Table 27). In these patients glucocorticoid therapy was started mostly within 2 weeks. In 6 patients hearing improved during therapy, but deteriorated later. No improvement of hearing occurred in 25 (74%) of the patients treated (Chapter 5).

Table 27. Improvement of hearing after glucocorticoid therapy in 37 TCS patients.

Glucocorticoid therapy	Improvement	No improvement	Total
Yes	9	25	34
No	2	1	3
Total	11	26	37

Effect on auditory symptoms in ACS

Of the 22 patients, 18 were treated with systemic glucocorticoids, the remaining patients with topical glucocorticoids only. In 4 (22%) permanent improvement of hearing was seen . In these patients glucocorticoid therapy was started, mostly within 2 weeks (see Chapter 5). In 4 patients, hearing improved during therapy, but deteriorated later. No improvement of hearing occurred in 14 (78%) of the ACS patients treated (Table 28).

Table 28. Improvement of hearing after glucocorticoid therapy in 22 ACS patients.

Glucocorticoid therapy	Improvement	No improvement	Total
Yes	4	14	18
No	2	2	4
Total	6	16	22

Spontaneous hearing improvement
In 1 TCS patient hearing improved after systemic glucocorticoid therapy was stopped and in another TCS case hearing recovered 2 days before glucocorticoids were started.
In 3/37 TCS patients who were not treated with systemic glucocorticoids, hearing did not improve in 1 patient, but improved spontaneously after 2 and 3 weeks, respectively, in the remaining 2 patients, treated with only topical glucocorticoids (Table 27). In 2 ACS patients hearing improved spontaneously after 2 and 3 weeks, respectively. Hearing did not recover in 2 other patients (Table 28).

Tinnitus and fullness in the ears
No conclusions can be made as to the effect of systemic glucocorticoids on tinnitus and fullness in the ears, as sufficient information on these symptoms is lacking.

For more detailed information and for conclusions about the audiological signs and symptoms, as well as for recommendations for treatment we refer the reader to Chapter 5.

Effect on systemic signs and symptoms
Most patients of both groups (22/37 TCS and 10/22 ACS) complained of more or less serious systemic symptoms. All patients recovered of their systemic symptoms and signs after treatment with glucocorticoids, with the exception of 1 ACS patient who died of a cardiac arrest.

Complications
Three patients had serious complications possibly because of long-term glucocorticoid therapy. One patient developed Eale's disease, another cataract and one retinal embolies.

4. Discussion and conclusions

In this retrospective study, the clinical data of 98 patients with presumed CS were investigated. According to our criteria (see Chapter 2) 37 of them were diagnosed as having TCS and 22 as having ACS. This is the largest group of patients published until now. The results are summarized in the following conclusions:

GENERAL FINDINGS

1) Sex distribution: Both in TCS and ACS no significant differences were found. Sex distribution was in favour of women in 5 other studies[1-3,5,7], whereas in one study[8,9] an equal sex distribution was found.

2) *Age:* Young adults are the main victims of CS. In TCS 90% of the cases were between 18 and 35 years of age and in ACS 73% belonged to this age group. These findings are in agreement with the literature,[1-3,5,7] although Vollertsen at al.[9] found a slightly wider range (80% between 14 and 47 years).

3) *Initial symptoms:* Ophthalmological symptoms were seen at onset in 37% TCS and in 45% ACS. Audiovestibular involvement in 26% versus 32%. In 26% of the TCS and 45% of the ACS patients both organs were affected simultaneously. Eyes and ears were both involved within 1.5 months in TCS, and within one month in ACS patients.

4) *Audiovestibular symptoms:* In most patients vertigo was the first audiovestibular symptom (43% in TCS, 23% in ACS). In a much smaller percentage, hearing loss occurred first (11% in TCS, 9% in ACS). This is in accordance with the literature.

5) *Prodromal symptoms:* Upper respiratory tract infections preceded onset in 43% of the TCS patients and in 27% of the ACS cases (No statistical difference; $p \approx 0.3$). This is in agreement with the literature.[1-3,5,7] Other prodromal factors were not found. Pregnancy has been suggested to precede CS[5]. Among 32 females only 2 were pregnant.

OPHTHALMOLOGICAL FINDINGS

6) *Interstitial keratitis:* In half the patients of both groups the focal peripheral opacities were described precisely. Unfortunately, in the other cases their location were not reported, although this is very important for the differential diagnosis of TCS and ACS.

7) *Corneal vascularization:* Severe interstitial keratitis leading to deep corneal vascularization was an uncommon finding. This is in agreement with the observations of Cobo and Haynes,[7] but in contradiction to the original description by Cogan.[2] The early administration of glucocorticoids, resulting in healing of the cornea, could explain this discrepancy.[2,7]
In one-quarter of the patients in both groups hyperaemic perilimbal vessels were observed. This symptom was seen at any time during the disease; it did not appear as a late phenomenon as has been claimed in the literature.[2,7]

8) *Exacerbations and remissions:* Exacerbations and remissions of the eye complaints were very common, in particular in TCS (TCS versus ACS: 63% versus 37%; $p \approx 0.01$). They are not always noticed, however, probably because of successful treatment with glucocorticoids and since the ophthalmological symptoms are of minor importance in very ill patients. Nevertheless, exacerbations and remissions of the ophthalmological symptoms are of great importance in diagnosing CS.

9) Conjunctivitis: We did not find conjunctivitis, but only conjunctival hyperaemia, whereas conjunctivitis was suggested in other studies.[3,59] The fact that only conjunctival hyperaemia was found in this study, is a strong argument in favour for a distinct eye inflammation as observed frequently in TCS.

AUDIOVESTIBULAR FINDINGS

10) Hearing loss: In about 40% of the patients a bilateral sensorineural hearing loss was found at onset. In 35% of them hearing impairment started unilaterally, though a bilateral loss developed within weeks. Eventually all, but 1 ACS patient, developed a bilateral (sensorineural) hearing loss. Total deafness occurred in 27% of the TCS and 19% of the ACS patients.

11) Tinnitus: Tinnitus was found in 84% of the TCS and 86% of the ACS cases. This is in accordance with the overall percentage of 77% given in the literature.[3,4,59]

12) Fullness in the ears: About one-third of the patients mentioned fullness in the ears (32% TCS and 33% ACS). The endolymphatic hydrops found in some histopathological studies[62,63] is most likely responsible for this phenomenon.

13) Vestibular symptoms: All patients complained of dysbalance, while 89% of the TCS and 95% of the ACS patients suffered from vertigo. One-third complained of ataxia. Postural instability usually persisted after treatment.

SYSTEMIC FINDINGS

14) General: Complaints such as fever, weight loss, fatigue, headache, arthralgia, myalgia and abdominal discomfort were common findings. The latter three symptoms were seen more frequently in ACS, but statistically there was no difference.

15) Cardiovascular: A systolic murmur was observed in 1/37 TCS patients, and aortic or mitralis insufficiency each in 1/22 ACS patients. No other serious cardiovascular signs were found. This is in contrast to the literature in which e.g. aortic insufficiency is frequently reported (Norton and Cogan:[3] 1/13; Haynes et al.:[5] 1/13; and Vollertsen et al.:[9] 3/18)
The finding that systemic symptoms in our patient groups were found less frequently may be explained by the fact that most patients were brought in by otorhinolaryngologists, whereas the patients of Haynes and Vollertsen came from the Departments of Rheumatology and Internal Medicine. When systemic diseases are observed, the patient will more likely be sent to an internist, whereas in cases of sudden deafness an otorhinolaryngologist will be consulted. Furthermore, serious systemic disease is

usually seen after a longer period of disease, when the signs and symptoms might be worse.[9] Nevertheless, in our study the average follow-up period in TCS is 3.7 years and in ACS patients 9.4 years, and serious systemic involvement has been rarely observed.

16) Testicular pain: Testicular pain was observed in 2/4 of the male patients seen by the author himself. A testicular biopsy taken from one of them revealed no abnormalities, in particular no vasculitis. This symptom was also described by Vollertsen et al.[9] Apart from our 2 cases it was recorded only once in the entire group of 28 male patients. It is remarkable that all 3 patients had TCS. Testicular pain is a minor symptom in very ill patients and may be overlooked.

LABORATORY FINDINGS

17) General: Elevation of the erythrocyte sedimentation rate and leukocytosis were common findings. This is in agreement with other studies.[9,5] No eosinophilia, thrombocytosis, liver, kidney and thyroid function impairment or abnormalities in electrolyte levels were observed.

18) Serum proteins and immunological tests: Serum protein levels, especially alpha-2-macroglobulin, is of uncertain significance. They are probably non-specific markers of inflammation.
In 4/4 patients (1 TCS and 3 ACS), corneal antibodies were found at onset, and in 1 patient also during an exacerbation of the disease (before glucocorticoid therapy). In 1 patient lymphocyte stimulation with specific eye extract was positive, while in 2 other patients this stimulation with inner ear extract was negative.

19) Biopsies: Biopsies (muscle, fascia, skin, vessels) were taken in 23/59 patients, but no abnormalities were found, in particular no vasculitis.

EFFECT OF GLUCOCORTICOID THERAPY

20) Eyes: The ophthalmological symptoms disappeared in less than 2 weeks in the majority of cases after glucocorticoid therapy was started, irrespective of whether this treatment was administered systemically, topically or in combination. Eventually, all eyes showed a total remission.

21) Ears: Improvement of hearing occurred in 9/34 TCS and 4/18 ACS patients. This was particularly seen in patients in whom therapy was started early (<1 week) after the onset of symptoms.
Haynes et al.[5,6] found improvement in hearing in 10/18 CS patients (55%) treated within the first 2 weeks after onset of hearing loss.

Early institution of glucocorticoid therapy is very likely of great importance for the final outcome of hearing in particular.

SPONTANEOUS IMPROVEMENT OF HEARING

22) Spontaneous improvement of hearing: In 4 patients spontaneous improvement of hearing occurred. This has been reported previously in CS,[2] but also in other diseases such as relapsing polychondritis[64] or polyarthritis nodosa.[65]

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CHAPTER 5

A RETROSPECTIVE STUDY OF AUDIOVESTIBULAR IMPAIRMENT IN COGAN'S SYNDROME

1- Introduction
2- Patients and methods
3- Audiological findings
4- Vestibular findings
5- Discussion and conclusions

1. Introduction

In his first paper on the syndrome now bearing his name, Cogan (1945) described the condition as a "nonsyphilitic interstitial keratitis associated with vertigo, tinnitus *or* hearing loss." However, as all patients demonstrated a sensorineural hearing loss, Norton and Cogan[2] later redefined this syndrome and included sensorineural hearing loss as an obligatory symptom.

Until now little attention has been paid to the audiological picture in Cogan's syndrome (CS). Usually only a sensorineural hearing loss is reported. The hearing loss is assumed to be of the cochlear type. Djupesland et al. [3] and Vermeersch et al.[4] found recruitment in their patients and observed temporary improvement of hearing after oral administration of glycerol. Békésy audiometry revealed the characteristics of cochlear hearing loss.[5] Two CS patients were reported to have developed a slight conductive hearing loss superimposed on the sensorineural hearing loss, after 1 and 4 years, respectively.[3]

The description of vestibular findings in CS is equally underrepresented. Most authors only report the presence of vertigo with nausea and vomiting in the early phase of the syndrome. Ataxia and loss of caloric response is a frequent finding.[6,7]

In this part of our study, the audiovestibular findings for 59 patients suffering from Cogan's syndrome will be analyzed.

2. Patients and methods

2.1. PATIENTS

The patients studied have been described in detail in Chapter 4. Of the 98 patients examined, 37 fulfilled our criteria of typical Cogan's syndrome (TCS) and 22 fulfilled those of atypical Cogan's syndrome (ACS).

2.2. METHODS

a) Audiometry

- Pure tone audiometry for air and bone conduction was performed in all patients several times during the course of the syndrome.
- Speech audiometry was carried out several times in all cases.
- Tympanometry was performed in 19 TCS and 12 ACS patients (results were classified according to the modified Jerger nomenclature.[8] as Type A: compliance: ≥ 0.2 ml, pressure: ≥ -100 mm H_2O; Type C_1: compliance: ≥ 0.2 ml, pressure: -100 to -199 mm H_2O).
- Recruitment tests (ABLB test-Fowler,[9] Békésy audiometry,[10] stapedial reflex test,[11] or Metz recruitment test[12]) were performed in 19 TCS and 8 ACS patients.

- Perstimulatory adaptation tests (tone-decay test,[13] Békésy audiometry) were carried out in 19 TCS patients and 1 ACS patient.
- Glycerol test[14] was performed in 9 TCS and 6 ACS cases.
- Brainstem-evoked response audiometry (BERA)[15] was carried out in 11 TCS and 6 ACS patients.

b) Vestibular function tests

In the majority of cases, vestibulo-spinal reflexes were examined by the Romberg test and the gait test. Electronystagmographic recording of spontaneous and positional nystagmus and responses on caloric stimulation (V.O.R.) was performed in 95% of the TCS and 96% of the ACS patients. A rotating chair nystagmogram was made in 19% of the TCS and 14% of the ACS patients.

c) Definitions and terminology

- Initial phase: phase of the syndrome before therapy.
- Stationary phase: phase of the syndrome in which the patient has recovered from his systemic and eye complaints and has a stable hearing loss without fluctuations.
- Hearing improvement/decrease: change in air-conduction threshold $\geq$ 10 dB.
- Initial hearing loss: hearing loss before therapy (Fletcher index).
- Grades of hearing loss (F = Fletcher index):
  1) slight and moderate loss: $F \leq 60$ dB,
  2) severe loss: $60 > F \leq 120$ dB; and
  3) deafness: $F > 120$ dB.
- High-tone hearing loss: hearing loss for frequencies above 1000 Hz.
- Low-tone hearing loss: hearing loss for frequencies below 1000 Hz.

3. Audiological findings

3.1 GENERAL FINDINGS

All 59 patients suffered from bilateral hearing loss, except for one patient with ACS who had a hearing loss in his right ear only. Tinnitus was a frequent symptom in both groups (TCS 84% and ACS 86%). One-third of the patients mentioned fullness in the ears (TCS 32% and ACS 33%). All patients, except those who became deaf, complained of fluctuations in hearing loss (Table 1).

Table 1. General auditory symptoms.

	TCS (N = 74 ears)	ACS (N = 43 ears)
Hearing loss	74 (100%)	43 (100%)
Fluctuations in hearing	68 (92%)	41 (95%)
Tinnitus	62 (84%)	37 (86%)
Fullness in the ears	24 (32%)	14 (33%)

3.2. SENSORINEURAL HEARING LOSS (PURE TONE AUDIOMETRY)

3.2.1 Initial hearing loss

a) Degree

In about 60% of both TCS and ACS patients, a slight or moderate hearing loss (≤ 60 dB) was measured in the initial phase before therapy was started. Severe losses were found in 30% and 21%, and total deafness in 10% and 14%, respectively (Table 2).

Table 2. Degree of initial hearing loss.

F (Fletcher index)	TCS (N = 74 ears)	ACS (N = 43 ears)
F ≤ 60 dB	45 (60%)	28 (65%)
60 < F < 120 dB	22 (30%)	9 (21%)
F ≥ 120 dB	7 (10%)	6 (14%)
Total	74	43

b) Audiometric curve

TCS

In Figure 1, the initial audiograms (before therapy) of all 74 ears of the 37 TCS patients are presented (deafness occurred in 1 patient bilaterally and 5 unilaterally). They are grouped according to the average hearing loss (Fletcher index). In the ears with slight losses, a small degree of low-frequency and high-frequency loss can generally be seen. In cases with greater hearing loss, the curves are sloping. Some patients show a combination of a low-frequency upslope and a high-frequency downslope, with a 'cut-off frequency' at 1000-2000 Hz. This curve type is even more frequent with average losses between 30 and 60 dB. The 'cut-off frequency' is then almost invariably found at 2000 Hz. With losses of more than 60 dB, the curves are less sloping. With very severe losses, only low-tone frequency have remained.

The curves analyzed above are the 74 initial audiograms, i.e. the audiograms made before therapy. Although they do not really illustrate the natural course of the syndrome, it is very likely that they depict how hearing proceeds in CS when no treatment is given.

ACS

In ACS, findings on the initial audiometric curves were similar to those in TCS, and are therefore not presented.

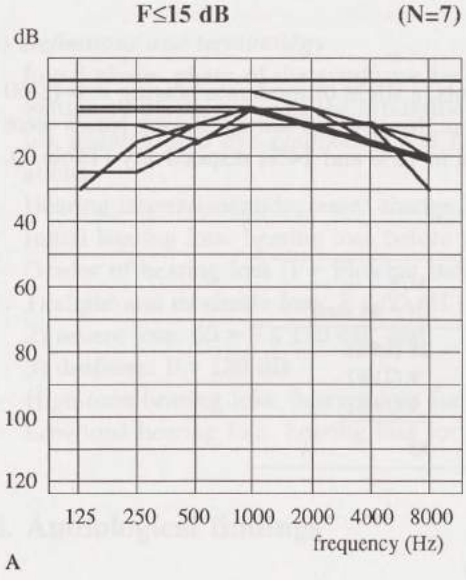
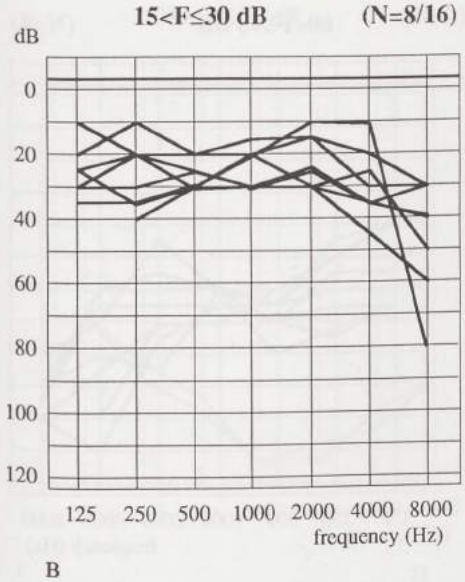
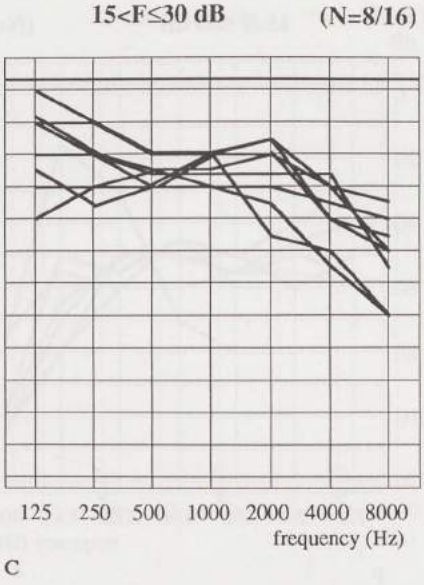


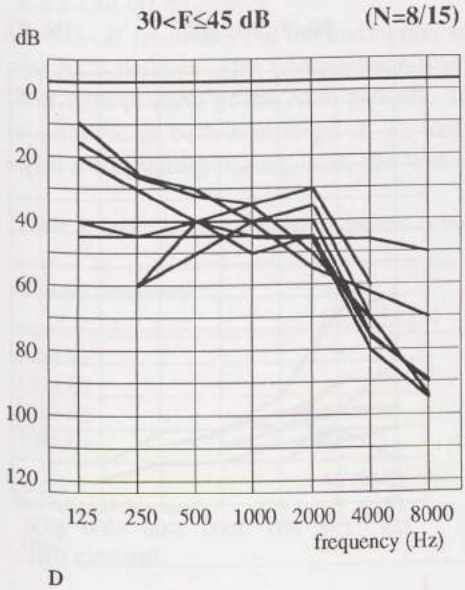
Fig.1 Initial audiograms of all TCS patients (N = 74 ears) grouped according to average hearing loss (F = Fletcher index): A: F ≤ 15 dB; B and C: 15 < F ≤ 30 dB; D and E: 30 < F ≤ 45 dB; F: 45 < F ≤ 60 dB; G: 60 < F ≤ 75 dB; H: 75 < F ≤ 90 dB; I: 90 < F ≤ 105 dB; J: 105 < F ≤ 120 dB; K: F > 120 dB.


15<F≤30 dB (N=8/16)
dB
0
20
40
60
80
100
120
125 250 500 1000 2000 4000 8000
frequency (Hz)

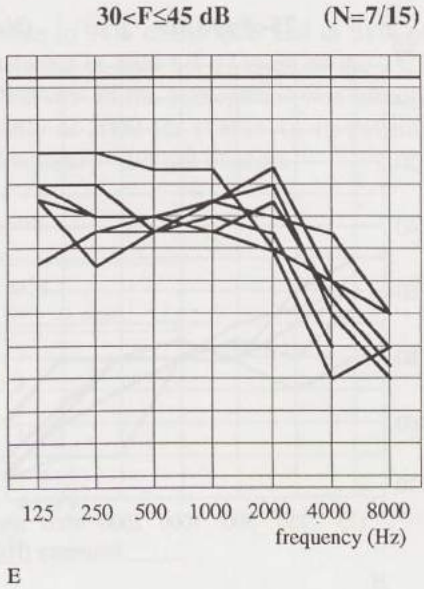
B


15<F≤30 dB (N=8/16)
125 250 500 1000 2000 4000 8000
frequency (Hz)

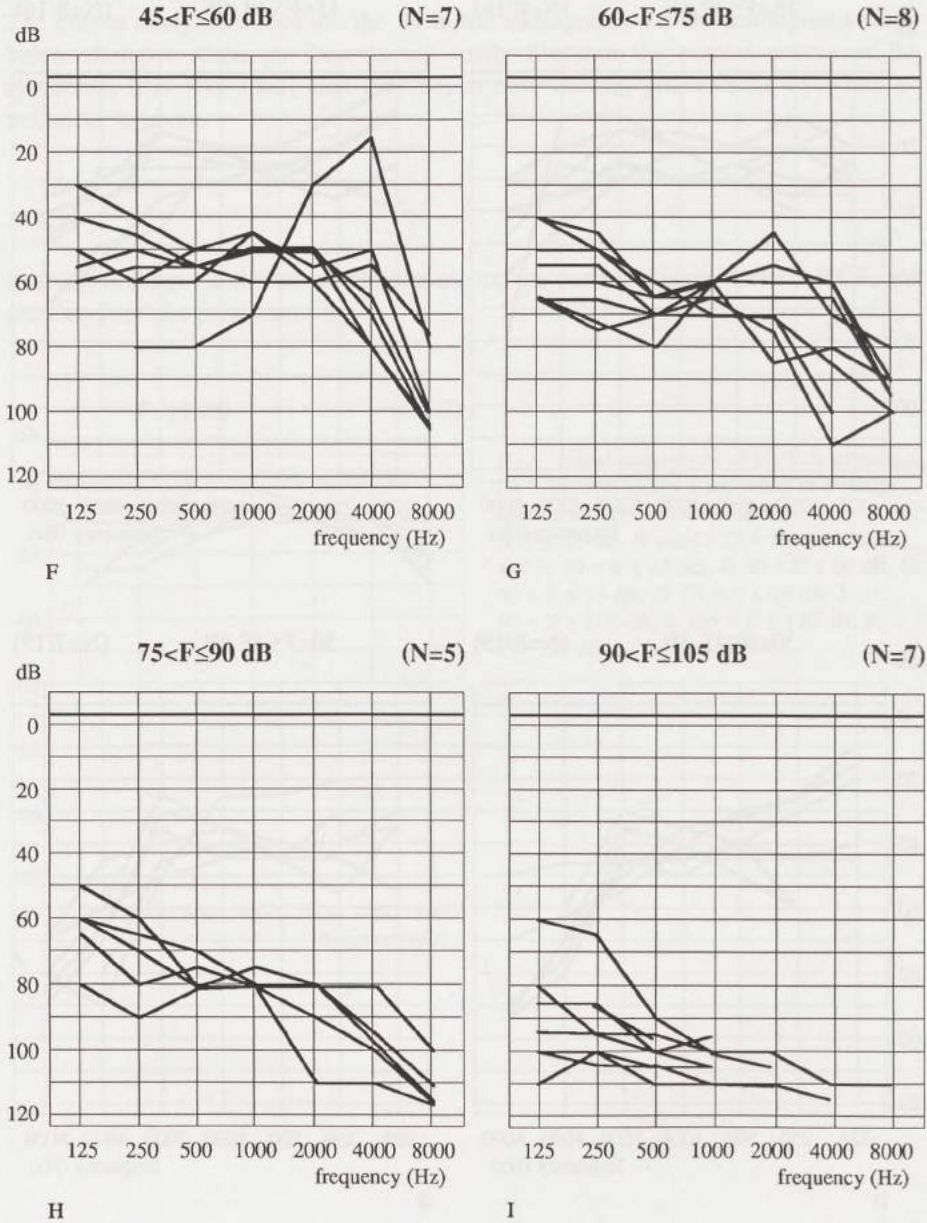
C

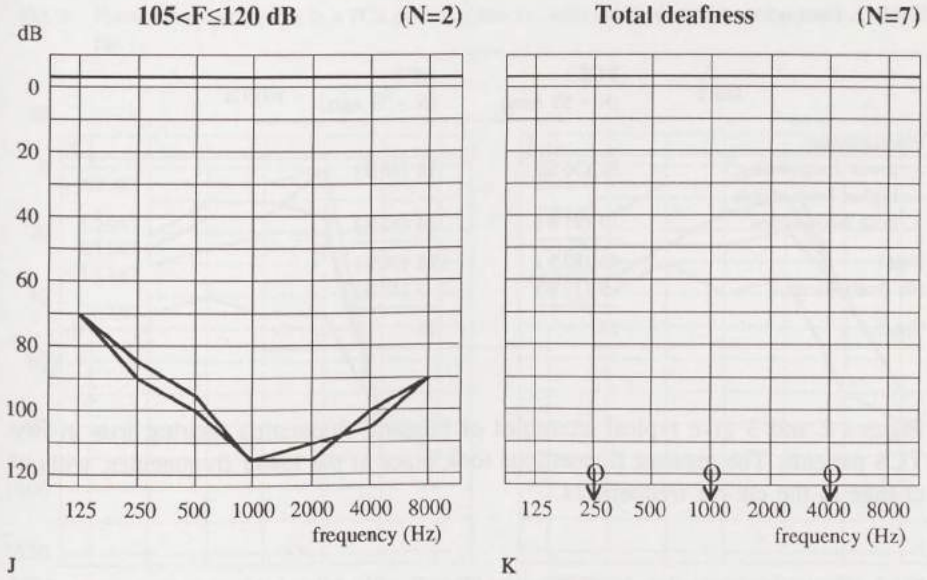

30<F≤45 dB (N=8/15)
dB
0
20
40
60
80
100
120
125 250 500 1000 2000 4000 8000
frequency (Hz)

D


30<F≤45 dB (N=7/15)
125 250 500 1000 2000 4000 8000
frequency (Hz)

E


45<F≤60 dB (N=7)
60<F≤75 dB (N=8)
75<F≤90 dB (N=5)
90<F≤105 dB (N=7)
dB
0
20
40
60
80
100
120
125 250 500 1000 2000 4000 8000
frequency (Hz)
F
G
H
I



3.2.2 Cut-off frequency

A 'cut-off frequency' in the audiogram was seen in 94% of the TCS and in 81% of the ACS patients. This phenomenon was not found in only 6% (3 ears) of the TCS and 19% (4 ears) of the ACS patients. The 'cut-off' in the audiograms was usually symmetric in both ears (Figs. 2, 3), and mostly at 2000 Hz (Table 4). In patients with a fluctuating hearing loss, the 'cut-off frequency' did not change.

Table 4. Localization of 'cut-off frequency' in audiograms.

'Cut-off frequency'	TCS (N = 49 ears)	ACS (N = 21 ears)
1000 Hz	7	3
1500 Hz	9	4
2000 Hz	27	9
4000 Hz	3	1
	46 (94%)	17 (81%)
No 'cut-off frequency'	3 (6%)	4 (19%)
Total	49	21

3.2.3 Fluctuations in hearing

In the majority of patients in whom sufficient follow up audiograms were available (TCS 83% and 90% ACS), fluctuations in hearing were measured, especially at the lower frequencies. Only a few patients did not show fluctuations in hearing (Table 3). In 19 TCS and 12 ACS patients no sufficient data were available.

Table 3. Fluctuations in hearing.

	TCS (N = 55 ears)	ACS (N = 31 ears)
Fluctuations:		
- lower frequencies	31 (56%)	14 (45%)
- higher frequencies	-	-
- both frequencies	15 (27%)	14 (45%)
Total	46 (83%)	28 (90%)
No fluctuations	9 (17%)	3 (10%)
Total	55	31

Figures 2 and 3 give typical examples of bilateral fluctuating hearing loss in two TCS patients. The greatest fluctuations took place at the lower frequencies, without change in the cut-off frequencies.

Fig. 2 Fluctuating hearing loss in a TCS patient (Case 1), with unchanged 'cut-off frequency' at 2000 Hz.

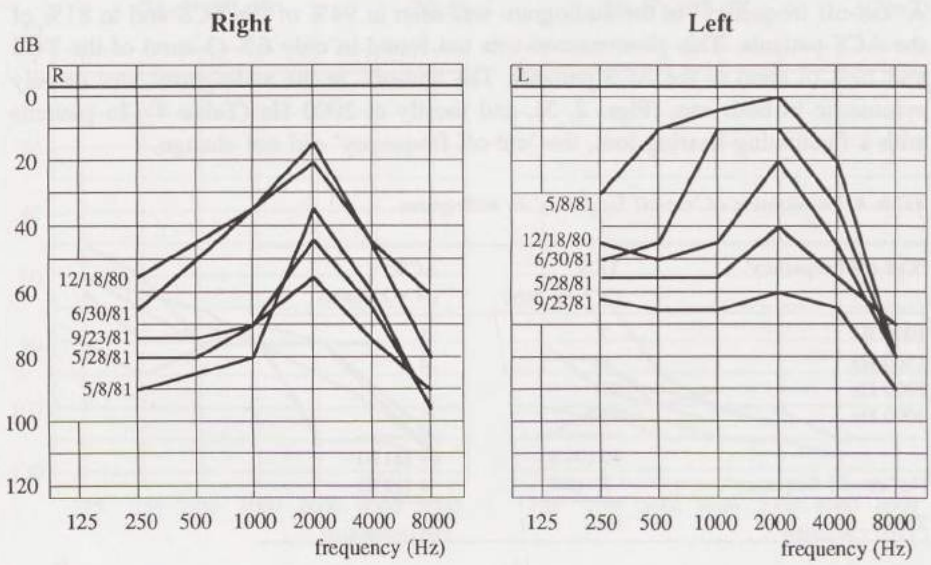
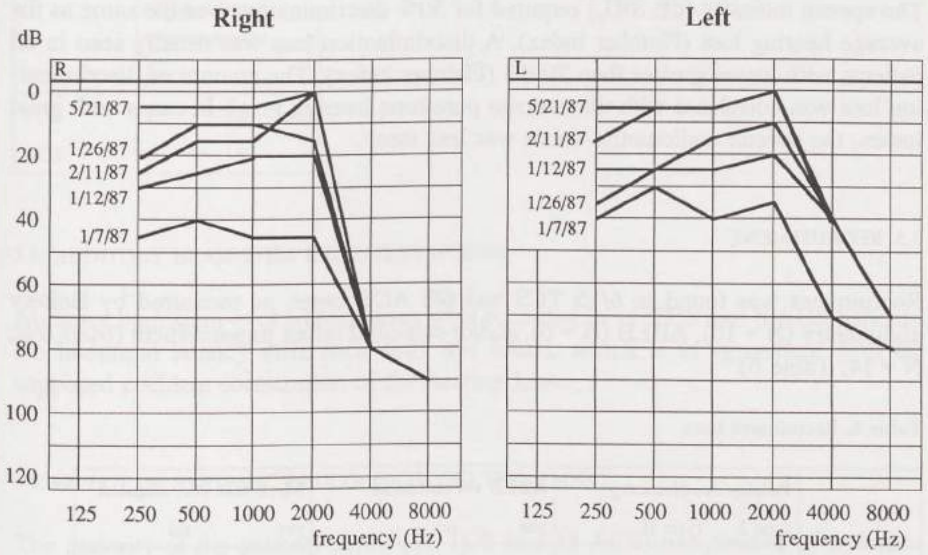


Fig. 3 Fluctuating hearing loss in a TCS patient (Case 2) , with unchanged 'cut-off frequency' at 2000 Hz.



3.3. CONDUCTIVE HEARING LOSS

a) Conductive hearing loss

Five TCS patients developed a slight (10–20 dB) conductive hearing loss, which was superimposed on the sensorineural hearing loss, after 2, 3, and 4 months, 1 and 4 years, respectively. In 3 of them, tympanometry was performed, which revealed a slightly decreased compliance of both ears (type C1). In the ACS patients, no evidence for conductive hearing loss was found.

b) Tympanometry and Stapedial Reflex

Tympanometry was normal (type A) in 16 out of the 19 TCS patients examined. In the other 3 TCS patients, tympanometry showed a slightly decreased compliance of both ears (type C1). In all 12 of the ACS patients, tympanometry had a normal result (Table 5). Stapedial reflexes were normal in all patients tested (8 TCS and 6 ACS; Table 5).

Table 5.

	Tympanometry		Stapedial reflex normal
	type A	type Cl	
TCS	16/19	3/19	8/8
ACS	12/12	0	6/6

3.4. SPEECH AUDIOMETRY

The speech intensity (dB SRL) required for 50% discrimination was the same as the average hearing loss (Fletcher index). A discrimination loss was usually seen in all patients with losses greater than 70 dB (Fletcher index). The amount of discrimination loss was correlated with the average pure-tone hearing level. In cases with great losses, the speech audiometric curve was less steep.

3.5. RECRUITMENT

Recruitment was found in 6/15 TCS and 6/8 ACS cases, as measured by Békésy audiometry (N = 10), ABLB (N = 6), and/or stapedial reflex measurement (Metz test; N = 14; Table 6).

Table 6. Recruitment tests.

	Békésy Audiometry		**ABLB recruitment**		**Metz test recruitment**	
	type I	type II	yes	no	yes	no
TCS	8/9	1/9	4/4	0	2/8	6/8
ACS	0	1/1	2/2	0	4/6	2/6

3.6. PER-STIMULATORY ADAPTATION

Per-stimulatory adaptation was found normal when measured by the tone decay test (N = 4) or by Békésy audiometry (N = 10; Table 7).

Table 7. Per-stimulatory adaptation tests.

	Békésy Audiometry		**Tone-Decay normal**
	type I	type II	
TCS	8/9	1/9	4/4
ACS	0	1	0

3.7. GLYCEROL TEST

A glycerol test was performed in 15 patients (9 TCS and 6 ACS). Some (10-20 dB) hearing improvement was measured in one TCS and one ACS patient. In the remaining cases, no effect was seen (Table 8).

Table 8.

	Glycerol test improvement	
	yes	no
TCS	1	8
ACS	1	5

3.8. AUDITORY BRAINSTEM-EVOKED RESPONSE

Auditory brainstem-evoked responses were recorded in 11 TCS and 6 ACS patients. No interaural latency difference shift was found, which is in agreement with the supposed cochlear localization of the hearing loss.

3.9. EFFECT OF SYSTEMIC GLUCOCORTICOID TREATMENT

The majority of the patients 52/59 (34 TCS and 18 ACS) was treated by systemic administration of glucocorticoids, in most cases with a daily dosage of > 1 mg/kg (Table 9).

Table 9. Systemic treatment of TCS and ACS patients.

Glucocorticoid treatment		Number of patients	
		TCS (N = 37)	ACS (N = 22)
systemic			
- daily dosage:	≥ 1 mg/kg	31 (84%)	18 (82%)
	< 0.8mg/kg	3 (8%)	0
	total:	34 (92%)	18 (82%)
- not systemic		3 (8%)	4 (18%)

3.9.1 Dosage-response effect

Most patients received high doses of systemic glucocorticoids (≥ 1 mg/kg/day; 76% TCS and 67% ACS). The remaining patients received lower doses (< 0.8 mg/kg/day) or no systemic glucocorticoids at all (Tables 9). In the patients treated with low-dose glucocorticoids (< 0.8 mg/kg), hearing always deteriorated.

3.9.2 Effect in relation to interval between first symptom and start of therapy

Hearing improvement was only seen in patients in which the interval between the initial symptoms and the start of systemic glucocorticoid therapy was short (within 2 weeks; Table 10).

- All 7 patients (TCS and ACS), in whom treatment was started within one week showed hearing improvement.
- Of the 6 patients who started therapy in the second week, only two showed hearing improvement.
- Of the 19 patients who started therapy after 2 weeks, hearing improvement was seen in two cases.

Table 10. Patients with TCS (N = 34) and ACS (N = 18) with improvement of hearing in relation to interval between therapy and initial symptoms.

	Improvement of hearing in relation to duration of therapy						**No improvement**	
Interval between therapy and initial symptoms (weeks)	1 week		2 weeks		> 2 weeks			
	TCS	ACS	TCS	ACS	TCS	ACS	TCS	ACS
1 week	4	1		1	1			
2 weeks	2			1			3	1
> 2 weeks	1						12	6
unknown			1			1	10	7
total	7	1	1	2	1	1	25	14

3.9.3 Effect in relation to duration of therapy

In the majority of the patients improvement of hearing was seen in the first week of treatment (Table 11).

Table 11. Patients with TCS (N = 34) and ACS (N = 18) with improvement of hearing in relation to duration of therapy.

	Improvement of hearing		**No improvement of hearing**	
Duration of therapy	TCS	ACS	TCS	ACS
1 week	7	1		
2 weeks	1	2		
> 2 weeks	1	1		
total	9	4	25	14

3.9.4 Characteristic examples of the course of hearing during therapy

Figure 4 shows a case with gradual complete restoration of a moderate (45 dB) sensorineural hearing loss during and after systemic glucocorticoid therapy of 80 mg/day for 2 weeks following by a tapering off in the 3^{d} and 4th week.

Figure 5 gives a typical example of a fluctuating hearing loss in relation to therapy. Some improvement occurred after 1 week 80 mg/day but hearing loss increased when this dosage was tapered off. After 2 weeks, when glucocorticoid dosage was increased to 40mg daily hearing improved considerably but deteriorated after the dosage was tapered again and stopped after 4 weeks. A new course of 60 mg glucocorticoids in combination with azathioprine resulted into a renewed hearing improvement.

In Figure 6 a case with gradual increase of hearing loss until total deafness in spite of 1 week therapy of 80 mg glucocorticoids daily is illustrated.

Fig. 4 Improvement of sensorineural hearing during glucocorticoid therapy in a TCS patient. (O: right ear; X: left ear).

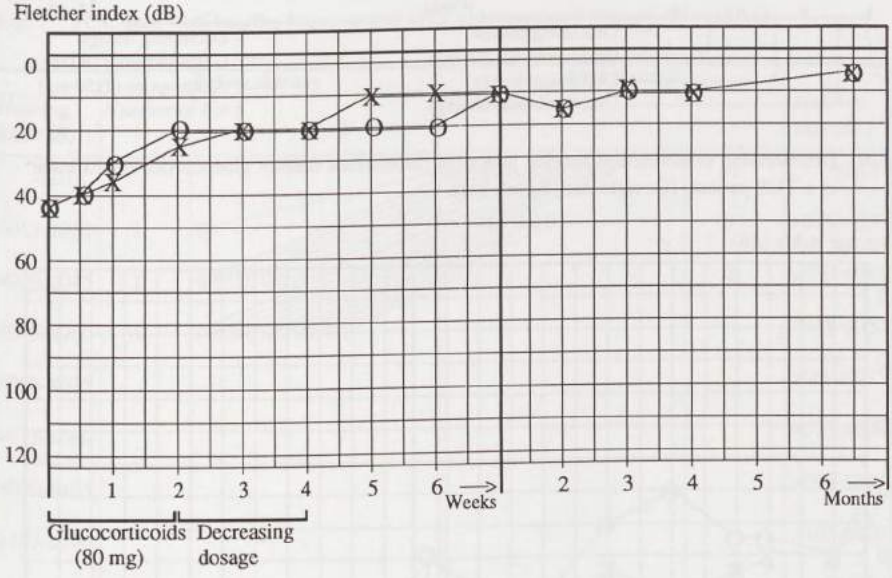


Fig. 5 Fluctuations in sensorineural hearing during glucocorticoid therapy in a TCS patient. (O: right ear; X: left ear).

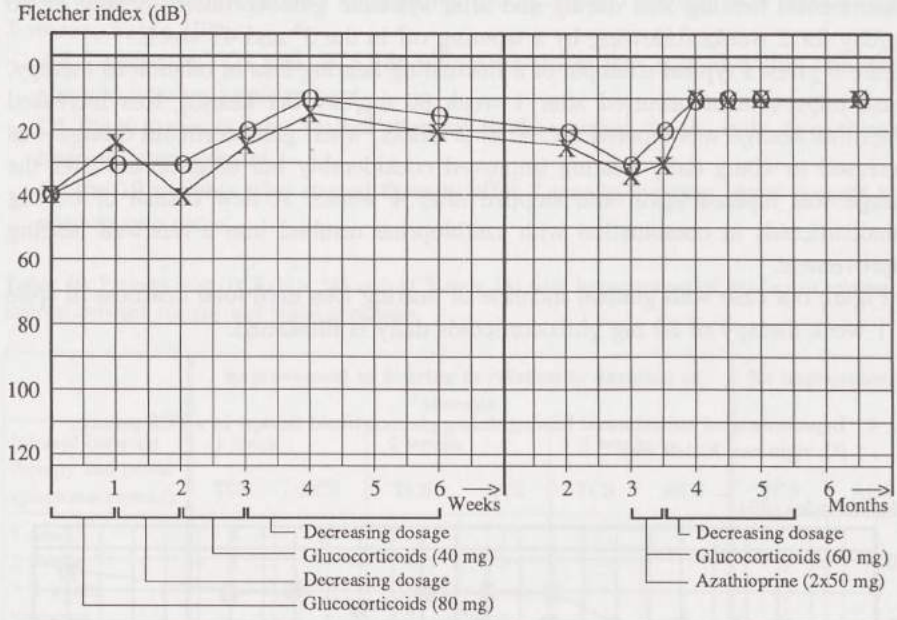
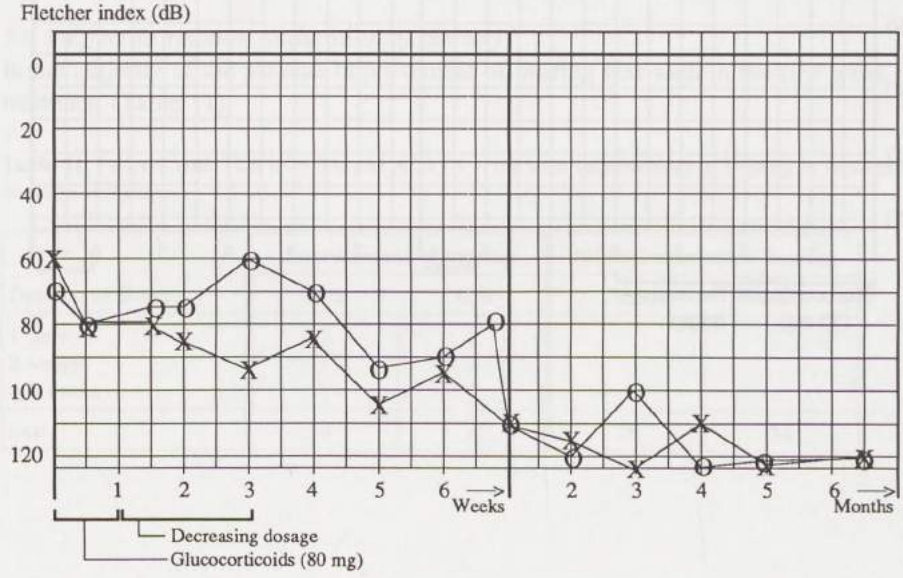


Fig. 6 Deteriorating sensorineural hearing loss with fluctuations despite glucocorticoid treatment in a TCS patient. (O: right ear; X: left ear).



3.10. HEARING LOSS AT STATIONARY PHASE

TCS

After therapy hearing recovered in 18 ears (9 patients). In 11 hearing was restored completely, in the other 7 ears a certain loss remained. In all cases in whom hearing improved initial loss was less than 60 dB (Fig. 7).
In 20 ears (10 patients) hearing remained unchanged in spite of treatment (Fig. 8).
In 30 ears (15 patients) further detoriation of hearing occurred in spite of the treatment given (Fig. 9).
In 6 TCS patients temporary improvement of hearing was seen during therapy, but their hearing loss at stationary phase was larger than the initial one.
Total deafness occured in 27% (7 bilateral and 6 unilateral) of the patients (Fig. 8 and 9).
An irreversible high-tone hearing loss was observed in 96% of the TCS patients with a slight, moderate, or severe hearing loss.

Fig. 7 TCS: Ears with hearing improvement after glucocorticoid therapy (N = 18/68).

	Before therapy		*After therapy*		
Hearing loss (dB)	*Number of Ears*		*Number of Ears*		*Hearing loss (dB)*
-≤015			00000000000	11	-≤015
>015-≤030	1	0	0 0000	5	>015-≤030
>030-≤045	7	0000000	00	2	>030-≤045
>045-≤060	10	0000000000			>045-≤060
>060-≤075					>060-≤075
>075-≤090					>075-≤090
>090-≤105					>090-≤105
>105-≤120					>105-≤120
>120					>120
Total	18			18	

Fig. 8 TCS: Ears not responding to glucocorticoid therapy (N = 20/68).

	Before therapy		*After therapy*		
Hearing loss (dB)	*Number of Ears*		*Number of Ears*		*Hearing loss (dB)*
-≤015	4	0000	0000	4	-≤015
>015-≤030	5	00000	00000	5	>015-≤030
>030-≤045	1	0	0	1	>030-≤045
>045-≤060	1	0	0	1	>045-≤060
>060-≤075	1	0	0	1	>060-≤075
>075-≤090	1	0	0	1	>075-≤090
>090-≤105	0			0	>090-≤105
>105-≤120	0			0	>105-≤120
>120	7	0000000	0000000	7	>120
Total	20			20	

Fig. 9 TCS: Ears with hearing deterioration in spite of glucocorticoid therapy (N = 30/68).

	Before therapy		*After therapy*		
Hearing loss (dB)	*Number of Ears*		*Number of Ears*		*Hearing loss (dB)*
-≤015	2	00			-≤015
>015-≤030	3	000			>015-≤030
>030-≤045	4	0000			>030-≤045
>045-≤060	5	00000	00	2	>045-≤060
>060-≤075	6	000000	0	1	>060-≤075
>075-≤090	4	0000	000000	6	>075-≤090
>090-≤105	4	0000	00	2	>090-≤105
>105-≤120	2	00	000000	6	>105-≤120
>120			0000000000000	13	>120
Total	30			30	

After therapy, hearing recovered in 3 patients bilaterally and 1 patient unilaterally. (Fig. 10).
In 4 ACS patients, temporary improvement of hearing was seen during therapy, but the hearing loss at stationary phase was larger than the initial one. There was no improvement of hearing in 6 patients treated with systemic glucocorticoids (Fig. 11). In 8 patients, a deterioration of hearing was seen despite glucocorticoid therapy (Fig. 12). Total deafness occurred in 19% (3 bilateral and 2 unilateral) of the patients (Figs. 11 and 12).
Only one ACS patient with a severe initial hearing loss (> 60 dB) showed improvement in hearing. In all other patients from this group (> 60 dB), hearing did not improve (Fig. 10).
An irreversible high-tone hearing loss was observed in 80% of the ACS patients with slight, moderate, or severe hearing loss.

In the stationary phase, 27% of the TCS (7 bilateral and 6 unilateral) and 19% of the ACS patients (3 bilateral and 2 unilateral) were completely deaf (Figs. 11 and 12).

Fig. 10 ACS: Ears with hearing improvement after glucocorticoid therapy (N = 7/35).

	Before therapy		*After therapy*		
Hearing loss (dB)	*Number of Ears*		*Number of Ears*		*Hearing loss (dB)*
-≤015			0 0 0	3	-≤015
>015-≤030	1	0	0 0	2	>015-≤030
>030-≤045	2	0 0	0 0	2	>030-≤045
>045-≤060	2	0 0			>045-≤060
>060-≤075	1	0			>060-≤075
>075-≤090	1	0			>075-≤090
>090-≤105					>090-≤105
>105-≤120					>105-≤120
>120					>120
Total	7			7	

Fig. 11 ACS: Ears not responding to glucocorticoid therapy (N = 12/35).

	Before therapy		*After therapy*		
Hearing loss (dB)	*Number of Ears*		*Number of Ears*		*Hearing loss (dB)*
-≤015	3	000	000	3	-≤015
>015-≤030	1	0	0	1	>015-≤030
>030-≤045					>030-≤045
>045-≤060	1	0	0	1	>045-≤060
>060-≤075					>060-≤075
>075-≤090					>075-≤090
>090-≤105					>090-≤105
>105-≤120	1	0	0	1	>105-≤120
>120	6	000000	000000	6	>120
Total	12			12	

Fig. 12 ACS: Ears with hearing deterioration in spite of glucocorticoid therapy (N = 16/35).

	Before therapy		*After therapy*		
Hearing loss (dB)	*Number of Ears*		*Number of Ears*		*Hearing loss (dB)*
-≤015	3	000			-≤015
>015-≤030	2	00	00	2	>015-≤030
>030-≤045	4	0000			>030-≤045
>045-≤060	1	0	00	2	>045-≤060
>060-≤075	2	00	0	1	>060-≤075
>075-≤090	1	0			>075-≤090
>090-≤105	3	000	000	3	>090-≤105
>105-≤120			000000	6	>105-≤120
>120			00	2	>120
Total	16			16	

3.11. SPONTANEOUS IMPROVEMENT

Of the 3/37 TCS patients who did not receive systemic glucocorticoids, hearing improved in two of them after 2 and 3 weeks, respectively. Both cases were only treated by topical administration of glucocorticoids in the eyes.
In 1 TCS patient hearing improved after systemic glucocorticoid therapy was stopped. In another TCS patient, hearing recovered 2 days before initial glucocorticoids were given.
Four out of 22 ACS patients did not receive systemic glucocorticoids. In 2 of them, hearing improved spontaneously after 2 and 3 weeks, respectively. Hearing did not recover in 2 other ACS patients.

3.12. IMMUNOSUPPRESIVE THERAPY (AZATHIOPRINE, CYCLOPHOSPHAMIDE)

In 18 patients (11 TCS and 7 ACS), immunosuppresive therapy, giving either azathioprine or cyclophosphamide, was combined with systemic glucocorticoid treatment. This combination therapy was administered when glucocorticoid therapy had previously failed or when it proved impossible to taper off the glucocorticoid dosage.
- In 14 cases, no improvement was seen.
- In 2 TCS and 2 ACS patients, hearing improvement was observed.

3.13. OTHER THERAPIES

In a small number of cases (2 TCS and 2 ACS), therapeutic attempts were undertaken using other types of drugs without simultaneous systemic glucocorticoids or immunosuppresive medication. Antihistamines (N=1), acyclovir (N=1), reomacrodex (N=1), and vasodilators (N=2) were administered. No hearing improvement was found.

4. Vestibular findings

4.1. GENERAL FINDINGS

Vertigo was the most common complaint, present in about 90% of the cases. It was usually accompanied by nausea and vomiting (Table 11). The remaining patients suffered from dysbalance only.

Table 11. Vestibular symptoms and signs.

	Number of patients	
	TCS (N = 37)	**ACS** (N = 22)
SYMPTOMS		
Vertigo	33 (89%)	21 (95%)
Nausea and vomiting	30 (81%)	18 (82%)
Dysbalance	4 (11%)	0

4.2. VESTIBULAR TESTS

Insufficient data were available concerning the results of vestibular function tests at the stationary phase. Therefore, we only present the initial findings.

TCS

a) Vestibulospinal reflexes

The Romberg test and gait test were performed in 16 patients. They showed dysbalance in 12 patients and no deviations in 4 patients. In 5/12 patients, no caloric function was found. A balance disturbance to one side was revealed by Romberg test and gait test in a direction opposite to the nystagmus. A balance disorder with complete loss of caloric response but without nystagmus was seen in 4/12 patients. One patient with a non-responding right labyrinth without nystagmus showed a properly positive Romberg test and gait test to the right.

b) Caloric test

The caloric test was performed in 35/37 (95%) patients. Complete bilateral loss of caloric response was found in 23 (66%) and a bilateral normal response in 4 (11%) patients. The other 7 patients had a decreased response (Table 12).

Table 12. Caloric response in TCS.

Caloric response of both labyrinths		**Patients** (N = 35)
None	None	23
None	Decreased	2
None	Normal	3
Decreased	Decreased	2
Decreased	Normal	1
Normal	Normal	4

c) Nystagmus

Spontaneous nystagmus was found in 17/35 patients. In 5 patients, the nystagmus was directed to the side with the better caloric response. In 3/4 cases with a normal caloric response, a nystagmus was present too (Table 13).

Table 13. Spontaneous nystagmus in TCS.

Caloric response of both labyrinths		Nystagmus towards side with		
		better response	worst response	undefined
None	None	-	-	7
None	Decreased	2	-	-
None	Normal	2	1	-
Decreased	Decreased	-	-	1
Decreased	Normal	1	-	-
Normal	Normal	-	-	3

A positional nystagmus was seen in only 2 patients with an unilateral loss of the caloric response. A complete loss of response, without spontaneous or positional nystagmus, was seen in 9 patients.

In 3/4 patients with a normal caloric response a nystagmus was found, indicating that the vestibular apparatus might have been involved in these patients. In the other patient, no nystagmus was recorded, but the rotating chair test showed a hypo-reaction, and slight abberations were found in the Romberg test.

d) Rotating chair test

The rotating chair test was performed in 7/35 patients. In 3 patients, this test was normal. A hypofunction was found in 4 patients (2 with no caloric response at all, one with a decreased, and one with a normal caloric response).

ACS

a) Vestibulospinal reflexes

The Romberg test and gait test were performed in 6 patients. Five patients with no caloric response had an abnormal Romberg and gait test. One of them had a spontaneous nystagmus, while 4 had no nystagmus.

b) Caloric test

The caloric test was performed in 21/22 (96%) patients. A bilateral complete loss of response was found in 13 patients (62%), and in 3 patients a normal response was measured (Table 14).

Table 14. Caloric response in ACS.

Caloric response of both labyrinths		Patients (N = 21)
None	None	13
None	Decreased	-
None	Normal	1
Decreased	Decreased	2
Decreased	Normal	2
Normal	Normal	3

c) Nystagmus

Spontaneous nystagmus was found in 8/20 patients. In 2 patients, the nystagmus was directed to the side with the better caloric response. No nystagmus was found in the 3 patients with a normal caloric reaction (Table 15).

Table 15. Spontaneous nystagmus in ACS.

Caloric response of both labyrinths		Nystagmus towards side with		
		best response	worst response	undefined
None	None	-	-	4
None	Decreased	-	-	-
None	Normal	1	-	-
Decreased	Decreased	-	-	1
Decreased	Normal	1	1	-
Normal	Normal	-	-	-

d) Rotating chair test

The rotatory chair test was performed in 5/21 patients. No response was recorded for 2 patients with no caloric reaction. A hypofunction was found in 2 patients (1 with no caloric response and 1 with a normal caloric reaction). A normal test was found in one patient with a normal caloric response.

4.3. CORRELATION BETWEEN VESTIBULAR FUNCTION AND HEARING LOSS

We compared the initial hearing loss levels with the initial bilateral caloric function. TCS and ACS patients were divided into four groups: (1) hearing loss ≤ 30 dB; (2) hearing loss > 30 dB - < 60 dB; (3) hearing loss ≥ 60 dB - < 90 dB; and (4) hearing loss ≥ 90 dB. We found no correlation (Table 16).

Table 16. Bilateral caloric a-reflexion and initial hearing loss.

Initial hearing loss	Number of patients TCS (N = 17)	ACS (N = 9)
≤ 30 dB	3	3
> 30 dB - < 60 dB	5	2
≥ 60 dB - < 90 dB	4	1
≥ 90 dB	5	3

4.4. VESTIBULAR FINDINGS AT STATIONARY PHASE

All patients with initial bilateral a-reflexion of the caloric response complained of a persisting postural instability. They suffered of balance disorders, especially in the dark and after fast head movements. Only in a few patients were these complaints confirmed by caloric testing. But unfortunately, we had insufficient data on the end of the disease.
In 3/8 TCS and 1/5 ACS patients with bilateral or unilateral hypofunction of the vestibular apparatus, we found compensation in the rotating chair. The remaining patients were not examined.

5. Discussion and conclusions

In this chapter the audiovestibular data of 59 patients with Cogan's syndrome (37 TCS and 22 ACS) have been analyzed. The results may be summarized by the following conclusions.

HEARING IMPAIRMENT

1) Sensorineural hearing loss: In all TCS and ACS patients, a sensorineural hearing loss was found, mostly at the same time in both ears. If started unilaterally, the hearing loss in the other ear developed within days.

2) Localisation of hearing loss: The sensorineural hearing loss was localized in the cochlea. Recruitment tests were positive in most cases. Per-stimulatory adaptation tests were always negative, and BERA showed no signs of retrocochlear involvement. The labyrinthine localization of CS was also confirmed by our CT- and MR-imaging studies.

3) Degree of sensorineural hearing loss: The degree of sensorineural hearing loss as found in the initial audiograms of all patients showed great variation, ranging

from a slight loss to a subtotal deafness. It is impossible to draw conclusions as to the natural course of the hearing loss from the initial audiograms, as they were made at various moments after onset of the disease.

4) Audiometric curve: In patients with a slight loss, commonly a small degree of low-tone and some high-tone loss was seen. In patients with a moderate loss, the audiometric curve was more sloping. In a great number of ears with a moderate loss, a combination of a low-tone upsloping curve and a high-tone downsloping curve with a 'cut-off frequency' was observed. In ears with a severe loss, the audiometric curves were invariably sloping without a cut-off frequency.

5) Cut-off frequency: The cut-off frequency in the audiogram was seen exclusively between 1000 and 2000 Hz, the latter being the most common localization of this phenomenon. This finding is not mentioned in the literature, but in some reports audiograms show similar curves.[17-20]
Cut-off frequencies have also been reported in other cochlear lesions, such as progressive hereditary deafness and ototoxicity. Apparently there is a major difference in the physiology of the low-tone and high-tone part of the cochlea. As suggested in earlier reports,[21,22] two systems can be distinguished in the cochlea: one for the lower frequencies, the other for the higher frequencies. .

6) Fluctuations in hearing: Sensorineural hearing loss was found to fluctuate in the majority of cases. In some patients, these fluctuations occurred spontaneously. In most cases they were seen during therapy and related to treatment.
Fluctuations were seen irrespective of the degree of hearing loss. Nonetheless, patients with slight and moderate losses generally demonstrated greater fluctuations than those with severe losses.

7) Low-tone hearing fluctuations: Fluctuations in hearing were particularly seen for the low frequencies. When we relate this finding to the observation: (1) that low-tone hearing loss is seen in particular in the early stages of the disease, (2) that many patients complain of fullness in the ears and, (3) that endolymphatic hydrops is found in temporal bone pathology studies of patients with CS, it seems likely that an endolymphatic hydrops plays a role in the early stages of Cogan's syndrome.

8) High-tone hearing fluctuations: High-tone hearing fluctuations were seen to a lesser extent than low-tone fluctuations. They mostly occurred in ears with slight and moderate losses.
Irreversible high-tone hearing loss was ultimately observed in 96% of the TCS and 80% of the ACS patients. We presume that high-tone loss in CS is a result of irreversible hair cell loss.[21,23]

9) Conductive hearing loss: In five TCS cases, a small degree of conductive hearing loss was found superimposed on the sensorineural hearing loss. In some patients a

slight decrease of middle ear compliance was measured at the same time. Stapedial reflexes were not found in these patients.
Some authors have reported a mixed hearing loss in Cogan's syndrome.[3,16] Because of the decreased compliance, Djupesland et al.[3] postulated that the conductive loss might be due to stapes fixation. If osteoneogenesis in the labyrinth represents a more advanced inner ear pathology in CS, and new bone formation is located in the vicinity of the oval window, stapes fixation might be imaginable.

10) Effect of treatment in relation to the interval between initial symptoms and start of treatment: Improvement of hearing after systemic glycocorticoid treatment was seen in 9/34 TCS and 4/18 ACS patients. Improvement in hearing was only seen when the interval between the initial symptoms and the start of treatment was short.
- All 7 patients in whom treatment was started within one week showed hearing improvement.
- Of the 6 patients who started therapy in the second week, only two showed hearing improvement.
- Of the 19 patients who started therapy after two weeks, hearing improvement was only seen in two cases.

This is an important finding, as it shows that the sooner systemic glucocorticoid treatment is started, the higher the chances for improvement and (complete) restoration of hearing.

11) Effect of treatment in relation to dosage: All patients who showed hearing improvement received a systemic glucocorticoid dosage of > 1 mg/kg a day. In all patients treated by a dosage of < 0.8 mg/kg, hearing deteriorated.

12) Effect of treatment in relation to degree of hearing loss: Improvement or restoration of hearing was only seen in ears with an initial loss of less than 60 dB. In patients with an initial hearing loss of more than 60 dB, hearing deteriorated in spite of therapy. This may be explained by the fact that all outer hair cells are degenerated which accounts for a loss of about 60 dB (provided that the majority of inner hair cells is still intact).[21,23]

13) Effect of immunosuppressive therapy: In 18 patients, immunosuppresive therapy (either azathioprine or cyclophosphamide) was added to systemic glucocorticoid treatment because of failure or insufficient response to glucocorticoid therapy. In 4/18 a positive effect was seen.

VESTIBULAR IMPAIRMENT

14) Caloric response: Caloric response was completely abolished in 28/35 TCS and 14/21 ACS patients. It was decreased (bilateral or unilateral) in 3 TCS and 4 ACS and normal in 4 TCS and 3 ACS patients; suggesting that the vestibular organ is

involved in the majority of cases. This is in accordance with the reports in the literature.[24]

15) Nystagmus: Spontaneous nystagmus was found in 17 TCS and 8 ACS patients. Because of this small number, no conclusions can be drawn. A positional nystagmus was found in only two patients.

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CHAPTER 6

CORNEAL AUTOIMMUNITY IN COGAN'S SYNDROME?

1- Introduction
2- Case reports
3- Discussion

Also published as: M.H.J.M. Majoor, F.W.J. Albers, R. van der Gaag, F. Gmelig-Meyling, E.H.Huizing. Corneal autoimmunity in Cogan's syndrome? Report of two cases. Ann Otol Rhinol Laryngol 101: 679-84, 1992.

Introduction

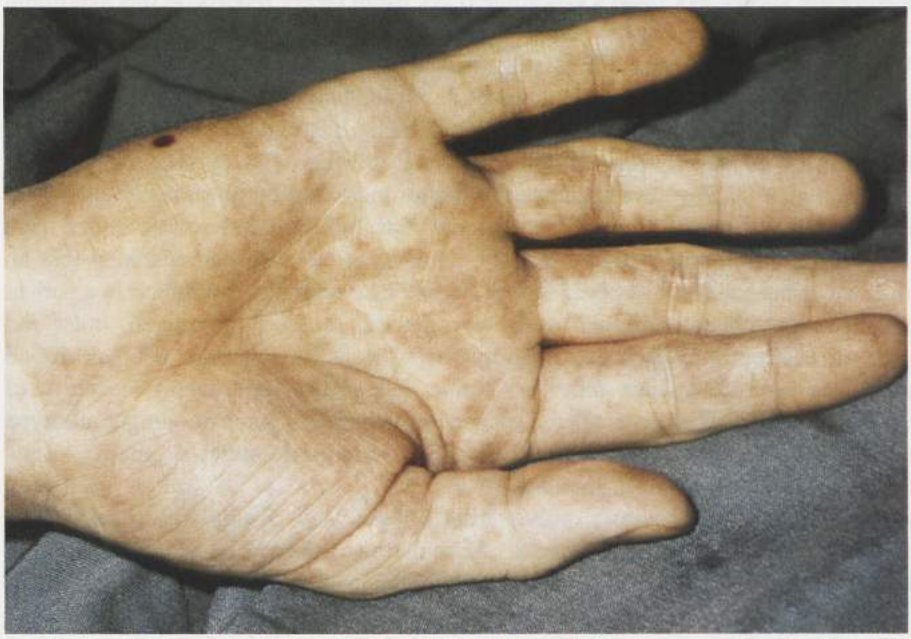
In 1945 the ophthalmologist David Cogan was the first to describe a syndrome of non-syphilitic deep interstitial keratitis with audiovestibular symptoms.[1] This disorder is currently known as Cogan's syndrome (CS). More recent reports on this syndrome have indicated involvement of other organ systems and systemic vasculitis.[2,3]
Although the aetiology of CS is still obscure, an immunological origin has been suggested by several authors. Hughes et al.[4] frequently found an elevation of the sedimentation rate in the acute stage of the disease. Edström and Vahlne[5] described a patient in an acute stage of the syndrome in whom an episode of transient immunological anergy was accompanied by an increased number of circulating T- and B-lymphocytes and signs of complement consumption. These observations were not confirmed in cases reported later.[4,6,7] Hughes et al.[4] also demonstrated that an inner ear membrane extract could induce lymphocyte migration inhibition in a patient with CS. Lymphocyte stimulation by eye-specific proteins (S antigen, outer rod segment, scleroprotein) was described by Peeters et al.[8] Arnold and Gebbers[9] found antibodies directed against inner ear tissue and corneal epithelium in serum of patients with CS. There is scattered evidence for human leukocyte-antigen allotype associations in CS, but the number of patients studied is still too small to draw significant conclusions from the data.[4,10]
In Wegener's granulomatosis, polyarteritis nodosa, and rheumatoid arthritis with corneal involvement, a high incidence of circulating antibodies to corneal epithelium has been observed, which suggests an autoimmune cause.[11]
In this paper one patient (Case 1) with typical (TCS) and one patient (Case 2) with atypical Cogan's syndrome (ACS) are presented. We used the definition of CS as formulated in Chapter 2. In both patients the disease was associated with systemic manifestations. During the course of the disease, tests were repeatedly performed to detect the presence of circulating antibodies against the cornea. The results support the possibility that autoimmune reactions contribute to the development of CS.

Case reports

Case 1. A 21-year-old man developed a mandibular absccess after extraction of a molar. Two days after drainage of the abscess he became very ill with severe headaches, poorly localized discomfort in the neck, lower back pain, and arthralgia, followed by abdominal discomfort 1 week later. He was admitted to the Department of Otorhinolaryngology, University Hospital Utrecht, 4 weeks after his first complaints. Besides the above-described symptoms, he had lost 12 kg in weight and suffered from febris intermittens, anorexia, fatigue, epistaxis, nausea and vomiting, and testicular pain. The patient complained of bilateral hearing loss with tinnitus and fullness in both ears. An equilibrium loss without vertigo was noticed when he changed position. Furthermore he suffered from pain in his eyes, photophobia, and conjunctival redness without diplopia.

On physical examination, thrombophlebitis of both legs and erythema of the palms of the hands and the soles of the feet were found (Fig. 1).

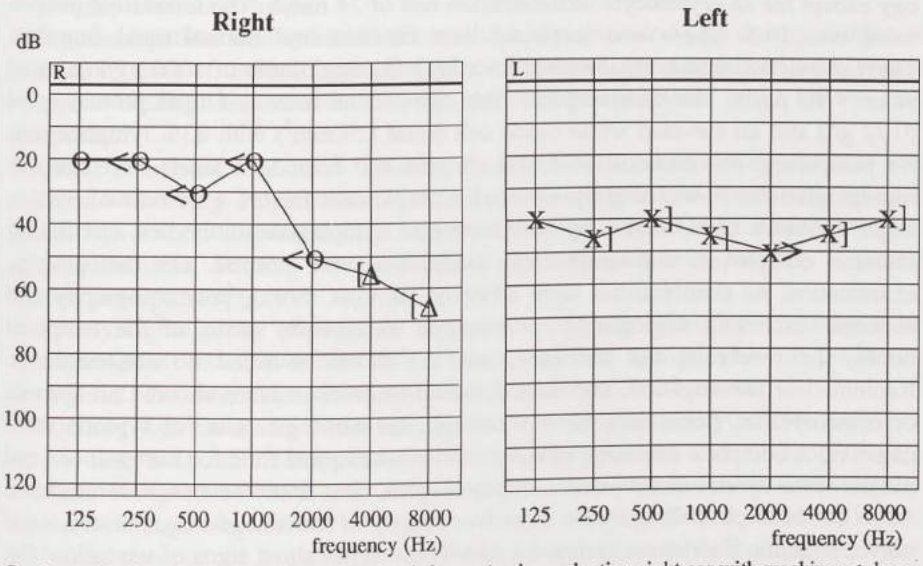
Fig. 1 Case 1. Erythema of the palms of the hand.



A loud systolic murmur was heard on abdominal auscultation. There were no neurologic aberrations. Routine otorhinolaryngological examination revealed no abnormalities and a normal tympanic membrane on both sides. Audiometry showed a slightly sloping sensorineural hearing loss of 30 dB for the right ear and of 45 dB for the left ear (Fig. 2). Similar losses were measured on speech audiometry, while speech discrimination was found to be normal.

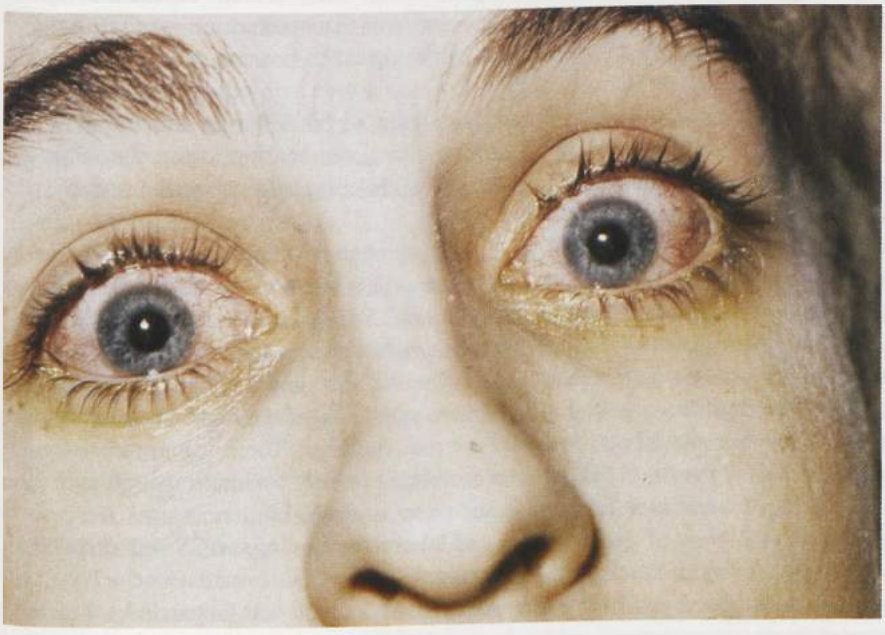
There was no recruitment, tone decay was normal, and Békésy audiometry was of the cochlear type. The glycerol test was negative and tympanometry was normal. The electronystagmography did not show spontaneous or positional nystagmus. On caloric examination, both labyrinths responded normally and symmetrically. A rotating-chair nystagmogram revealed hypofunction. On ophthalmological examination, interstitial keratitis with hyperaemic perilimbal vessels and conjunctival hyperaemia was observed (Fig. 3).

Fig. 2 Case 1, Pure tone audiometry.



O: air conduction right ear; X: air conduction left ear. Δ: air conduction right ear with masking; <: bone conduction right ear; >: bone conduction left ear; [: bone conduction right ear with masking;]: bone conduction left ear with masking.

Fig. 3 Case 1. Injected perilimbal vessels and conjunctival hyperaemia of both eyes.



Routine laboratory findings showed normal values of blood chemistry and haematology except for an erythrocyte sedimentation rate of 74 mm/h. The C-reactive protein value was 14.6. There was increased liver function and normal renal function. Thyroid function was normal except for a high thyreoglobulin of 1000 µg/l (normal value < 10 µg/l). The cerebrospinal fluid showed an increased total protein level (0.72 g/l) and an elevated white blood cell count (29/mm^3) with 83% lymphocytes. No paraprotein was demonstrable, and albumin and fibrinogen levels were normal. Immunoglobulin A was slightly elevated. Complement factors were normal, with a slight elevation of C3 and C1q. Antineutrophil cytoplasmic antibodies, circulating immune complexes, and antinuclear antibodies were normal. On radiographic examination, no abnormalities were observed (sinuses, thorax, polytomography and abdomen including angiography). Computed tomography scans of the temporal bones, the cerebrum, the abdomen, and the thorax revealed no abnormalities. Radionuclear investigation, and leukocyte and technetium scans showed no abscess or osteomyelitis. Bone marrow was normal, and serologic tests for syphilis were negative. A complete screening of serum and cerebrospinal fluid for bacterial or viral causes of the syndrome revealed a herpes simplex virus titer elevation in serum from 16 to 64. Multiple cultures were negative. Biopsy of the skin, fascia, muscle, sural nerve, jejunum, duodenum, pancreas, and liver did not show signs of vasculitis. On the basis of these clinical and laboratory findings, TCS was diagnosed.
Initial treatment with broad-spectrum antibiotics was unsuccessful. After systemic administration of a high dosage of corticosteroids (60 mg prednisone daily), the condition of the patient improved significantly. Before corticosteroid therapy, there was a slight improvement of hearing in both ears, which continued during corticosteroid therapy. The keratitis was cured with betamethasone eye drops. After 7 months, the hearing level in both ears had returned to normal.

Case 2. An 18-year-old man suffered from pain in his left eye with redness and photophobia, followed by vertigo, vegetative reactions, hearing loss and tinnitus the next day. Two weeks later an exacerbation of his complaints occurred and he was admitted to a local hospital.
Otological examination revealed a normal tympanic membrane on both sides. Audiometry showed a flat sensorineural hearing loss of about 90 dB for the right ear and a sloping sensorineural hearing loss of about 50 dB for the left ear. Ophthalmological examination revealed an interstitial keratitis and uveitis of the left eye only. Visual acuity was normal in both eyes. There were no neurological aberrations. Cerebrospinal fluid analysis and computed tomography of the cerebrum and petrous portion of the temporal bone revealed normal findings. The erythrocyte sedimentation rate was 6 mm/h, in the presence of leukocytosis without eosinophilia. The results of renal and liver function tests were normal. Immunological tests were negative. On the basis of these clinical and laboratory findings, ACS was diagnosed. The patient was first treated with high systemic doses of dexamethasone acetate and betamethasone eye drops. After 2 weeks the treatment was expanded to include plasmaphoresis three times weekly. In spite of this treatment the clinical situation

worsened, and he was referred to the Department of Otorhinolaryngology at the University Hospital Utrecht.

The general patient history included eczema on the arms and legs during childhood and complaints of asthma with allergy and hayfever. On admission there was a complete hearing loss and severe vertigo, whereas the symptoms in the left eye had diminished.

Physical examination showed a young man with a Cushingoid appearance and asthmatic wheezing. Palpatation of the abdomen was painful, and there was myalgia of the legs without arthralgia. Routine otorhinolaryngological examination revealed no abnormalities. Hearing loss was 100 dB in both ears, with severely impaired speech perception (Fig. 4).

Electronystagmography showed no response to caloric stimuli or rotating-chair nystagmogram tests on either side. There was no spontaneous or positional nystagmus. The interstitial keratitis of the left eye was almost cured.

Laboratory data showed a leukocytosis without eosinophilia. Erythrocyte sedimentation rate, liver and kidney function, and serum albumin and fibrinogen were normal. Paraproteins were not demonstrable. Immunoglobulin M was slightly elevated. Complement factors were normal, as were cryoglobulins. Autoantibodies, including rheumatoid factors and antineutrophil cytoplasmic antibodies, were not demonstrable. Some circulating immune complexes were present; the test for antiperinuclear factor was weakly positive. Serologic tests for syphilis were negative. Screening of serum for bacterial or viral infections was negative. A radiographic examination revealed no abnormalities.

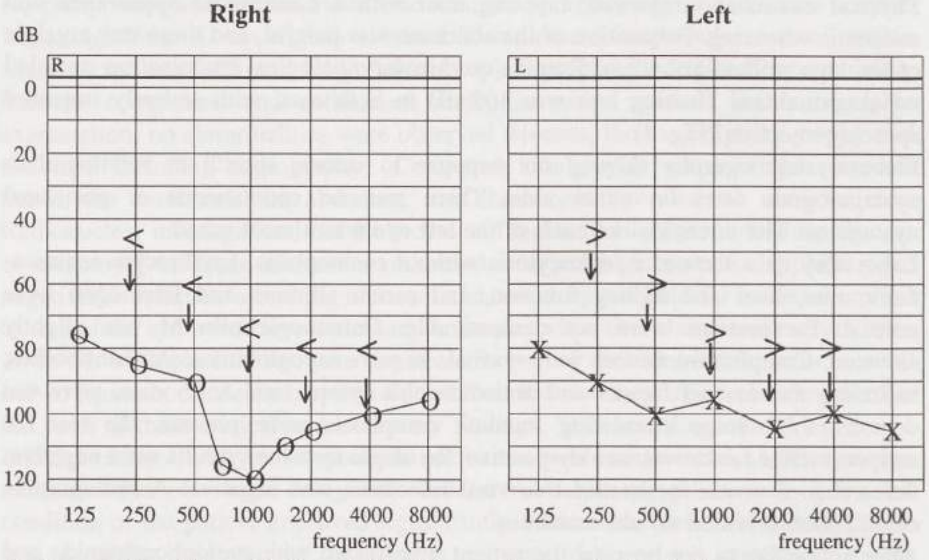
After admission to our hospital the patient was treated with cyclophosphamide and prednisone (during the first week, 50 mg and 25 mg, respectively, daily; during the second week, 100 mg and 25 mg, and during the third week, 150 mg and 25 mg). Meanwhile betamethasone eye drops were given three times a day. Because of a slight improvement in hearing, a maintenance dosis of 15 mg prednisone daily was given. In the meantime a hearing aid was prescribed.

Four months later his clinical condition worsened again, with hearing loss on both sides and retroauricular pain. The patient complained of pain in the right eye (especially during eye movement), general illness, fatigue, headaches, arthralgia, and abdominal pain. An audiological investigation revealed a loss of 120 dB on the right and 110 dB on the left. A routine ophthalmologic examination showed conjunctival hyperaemia of the right eye with hyperaemic perilimbal vessels but no interstitial keratitis. Scleral thickness of the right eye was demonstrated by computed tomography. An episcleritis was suggested. Except for an erythrocyte sedimentation rate of 50 mm/h and a leukocytosis, the routine laboratory data were normal. Immunological research revealed slightly elevated C1q, immunoglobulins G and M, positive immune complexes (immunoglobulins G and M), and a slightly positive antiperinuclear factor.

Because of this exacerbation, the patient was treated with a high dosage (1 g) methylprednisolone for 3 days and of atropin sulfate and dexamethasone-neomycin-polymyxin eye drops. In spite of the treatment, no improvement in the hearing

occurred. Further therapy was discontinued. After 3 months his general condition stabilized, with disappearance of the eye complaints.
Subtotal deafness, a slight tinnitus, and postural instability persist. The patient is supporting his lipreading by means of a body hearing aid.

Fig. 4 Case 2, Pure tone audiometry.



O: air conduction right ear; X: air conduction left ear. <: bone conduction right ear; >: bone conduction left ear.

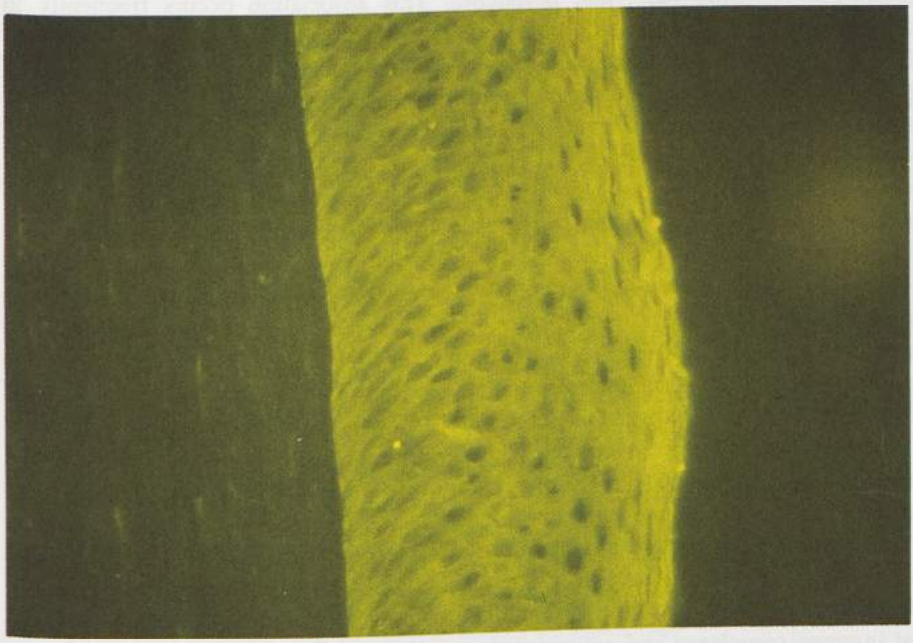
ANTIBODIES AGAINST CORNEAL ANTIGENS

Apart from the general immunologic investigations, we determined the presence of circulating corneal antibodies in the serum of both patients. Sera were obtained at the time of admission to our hospital, as well as before and after each treatment. As controls, blood samples were taken from two healthy young adults. Both control subjects were questioned concerning their previous medical history; there had been no otological or ophthalmological complaints, and they had no history of contact lenses or of working or living in airconditioned spaces. Circulating antibodies to corneal epithelium were assayed by an indirect immunofluorescence technique on bovine cornea. The sections were scored blindly by two investigators using the following classification: strongly positive (Fig. 5), positive, and negative. Two types of immunofluorescence in the corneal epithelium were observed:

1) staining of cell membranes only, and
2) cytoplasma plus cell membrane staining. In addition, staining of the keratocytes was seen in the stroma.

The methods used have been described previously by Van der Gaag et al.[12] and Kruit et al.[11]

Fig. 5 Case 1. Strongly positive immunofluorescence on bovine cornea.



In Case 1, prior to corticosteroid therapy, the immunofluorescence was strongly positive for the cytoplasm and slightly positive for the cell membranes of the corneal epithelium. Moreover, there was staining of keratocytes in the stroma. Five days after systemic corticosteroid administration, the immunofluorescence still showed positive staining of the cytoplasma in the epithelium and keratocytes in the stroma, but the staining of the cell membrane had become negative.
In Case 2, the patient had already been treated by corticosteroids and plasmaphoresis in a local hospital before immunological investigations could be carried out. During the first weeks following admission, the results of immunofluorescence tests on bovine cornea were negative. When his clinical condition worsened, immunofluorescence in the epithelial layer of the cornea was strong, but no staining of keratocytes was found. The staining of the cornea remained positive after treatment with a high dose of methylprednisolone. No circulating corneal epithelium antibodies were found in either of the controls.

Discussion

In both patients, the characteristic symptoms of TCS and ACS were associated with systemic disease such as abdominal discomfort, anorexia, vegetative reactions, arthralgia, testicular pain, and headaches. This association occurs frequently in autoimmune disease. Our study of immunity against corneal antigen, as assayed by indirect immunofluorescence, may provide evidence for an immunological cause of this syndrome. In Case 1, antibodies to corneal epithelium and keratocytes in the stroma were found before treatment with corticosteroids. Five days after corticosteroid treatment was started, the cytoplasm and stroma cells were still positive, whereas the cell membranes were negative. In Case 2, no antibodies to corneal antigens were found when the patient was admitted to our hospital after his initial treatment elsewhere with dexamethasone and plasmaphoresis. Following an exacerbation of the disease, a strong serum reactivity to the epithelial layer of the cornea was observed. After therapy with high-dosage methylprednisolone, the reactivity decreased. There seems to be a correlation among the therapy given, the clinical condition of the patients, and the presence of antibodies to the cornea. Immunity to corneal antigens has been described previously in patients with CS.[8,9,13] Those findings were not correlated with the therapy given; however, Hughes et al.[4] reported positive results of tests for lymphocyte migration inhibition and transformation during the acute stage of the disease. These results did not show any correlation with corticosteroid therapy. In agreement with other investigators, we found nonspecific immunologic and haematologic phenomena in the acute phase of the disease: a slight elevation of immunoglobulins M and G and C1q; the presence of immune complexes and antiperinuclear factor; an elevated erythrocyte sedimentation rate; and leukocytosis with neutrophilia.[4-9]

In both TCS and ACS, there is always interstitial keratitis.[6,7,14] In our patients, however, the immunofluorescence of the epithelium was stronger than that of the stroma. This finding cannot be explained by our present knowledge. It might be the result of the fact that the corneal epithelium is the richest reservoir of antigens,[15] whereas the relatively a-cellular stroma provides a more limited source of antigens. In both patients, there was an amelioration of the ophthalmological symptoms after topically and systemically administered corticosteroid therapy; this is in agreement with the literature.[6,7] The first patient had a slight improvement of hearing in both ears before administration of corticosteroids, and the improvement continued during therapy. Seven months later, the hearing level in both ears had returned to normal. The second patient did not show any improvement in response to the various medications given. It is not known whether the hearing loss is self-limiting, as suggested by our first case. Most CS patients are treated with a high-dosage of corticosteroids at an early stage of the disease. Vollertsen et al.[6] and Hughes et al.[4] found an amelioration of hearing in approximately 40% of the patients who were treated with systemically administered corticosteroids.

Patient 1 developed an abscess in the mandibula 2 days before the initial symptoms appeared. We also found an elevated titer of herpes simplex in this case. Patient 2

suffered from eczema, asthma, and allergic rhinitis. It is possible that the anticorneal antibodies are secondary to tissue damage, induced by unknown cause. Although consistent evidence of infection is not found in the literature, a viral or bacterial cause of CS has often been postulated.[5,6,16,17]

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CHAPTER 7

CORNEAL AUTOIMMUNITY IN A PATIENT WITH RELAPSING POLYCHONDRITIS

1- Introduction
2- Case report
3- Discussion

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Introduction

Relapsing polychondritis is a recurrent systemic disease, which is characterized by episodic inflammation of cartilaginous structures. The first case of relapsing polychondritis was described in 1923 by Jaksch-Wartenhorst,[1] who used the term "polychondropathia." In 1960 Pearson et al.[2] reviewed 10 cases and introduced the name "relapsing polychondritis." To date, approximately 300 cases of relapsing polychondritis have been reported in general reviews.[1-9] In addition, case reports of relapsing polychondritis with specific manifestations have been published.[10-20]
In a prospective study of 23 patients and a review of 136 reported cases, McAdam et al.[7] proposed the following diagnostic criteria for relapsing polychondritis:

1. bilateral auricular chondritis,
2. non-erosive inflammatory polyarthritis,
3. chondritis of the nasal cartilages,
4. ocular inflammation (conjunctival hyperaemia, keratitis, scleritis, uveitis),
5. respiratory tract chondritis affecting laryngeal and tracheal cartilages,
6. audiovestibular symptoms (sensorineural hearing loss, tinnitus, vertigo).

The diagnosis of relapsing polychondritis is certain when three or more of the six clinical features are present with positive histological confirmation. Damiani and Levine[4] further modified the diagnostic criteria into the following:

1. three or more of McAdam's criteria,
2. one or more of McAdam's criteria with positive histological confirmation,
3. chondritis in two or more separate anatomical locations, with response to steroids or diamino-diphenylsulfone (dapsone).

Histological examination of biopsied cartilage in relapsing polychondritis shows certain characteristic features. The histopathological changes initially consist of a decreased basophilic staining of cartilage matrix and a loss of matrix acid mucopolysaccharides. Subsequently, the cartilage shows secondary chondral and perichondral inflammation with decreased numbers of chondrocytes, lacunar breakdown, and infiltration of neutrophils. Finally, destruction of the cartilage with replacement by fibrous tissue is observed.[3,4,7,8]
Although the aetiology of relapsing polychondritis is still unknown, autoimmune mechanisms are likely. In Cogan's syndrome, Wegener's granulomatosis, polyarteritis nodosa, and rheumatoid arthritis with corneal involvement, a high incidence of circulating antibodies to corneal epithelium has been observed, suggesting an autoimmune pathogenesis of these diseases.[21-24]
We report a patient with relapsing polychondritis, in whom the presence of circulating corneal antibodies was determined before and after treatment. These findings provide further evidence for an immunological aetiology of the disease.

Case report

A 60-year-old woman was admitted to the University Hospital of Ghent with complaints of recurrent tenderness and redness of both ears accompanied by pain and swelling of the nose. At the same time the patient had experienced irritation of both eyes with blurring of vision. She also presented with a slight inspiratory stridor associated with a nonproductive cough. Besides these symptoms she suffered from anorexia, nausea, fatigue, lower extremity arthralgia, and weight loss of 11 kg. Past medical history included diabetes mellitus type II without requiring medication.
Physical examination revealed an acute chondritis of both auricles with some loss of cartilage and extremely narrowed external auditory canals (Fig. 1). A saddle deformity of the nose was present due to loss of septal cartilage (Fig. 2). However, endoscopic examination of the larynx was unremarkable.

Fig. 1 Acute chondritis of the auricle with deformity of the cartilage and a narrowed external auditory canal.

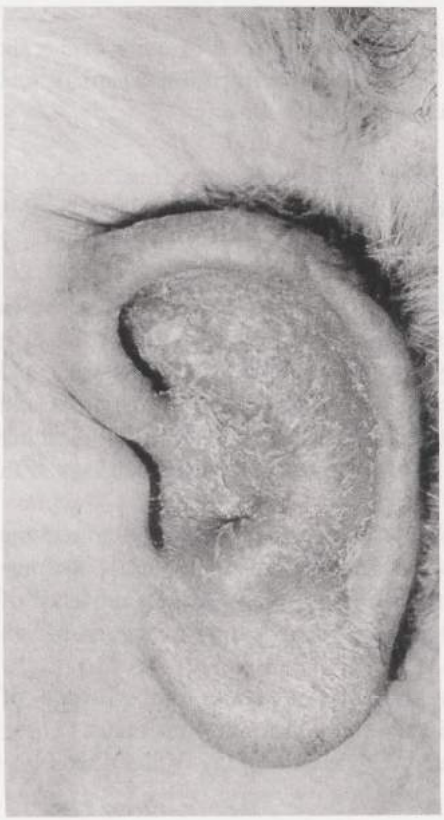
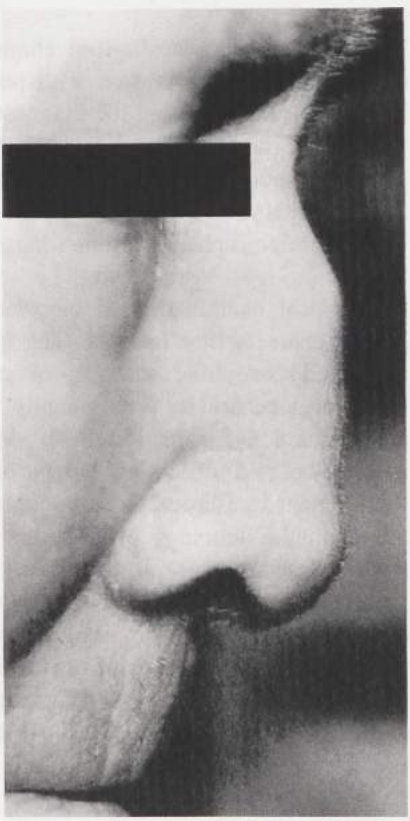
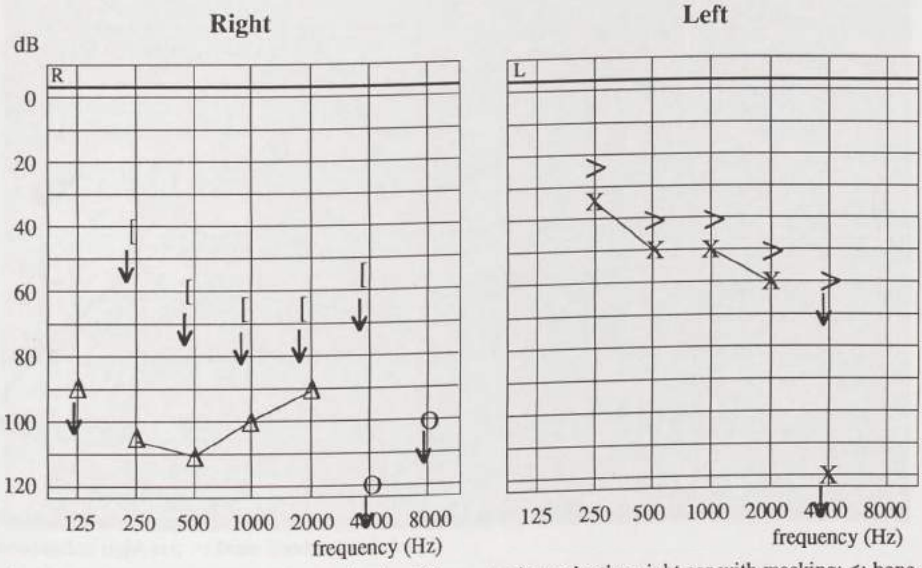


Fig. 2 Deformity of the nose due to loss of septal cartilage.



On ophthalmological examination interstitial corneal edema associated with corneal-guttata, ciliary, conjunctival and episcleral hyperaemi was observed in the right eye only.
Shortly after admission the patient developed sudden deafness in both ears with tinnitus and vertigo. On otological examination normal tympanic membranes were observed. Audiometry showed complete bilateral sensorineural hearing loss with absent speech discrimination (Fig. 3). Bilaterally no response was found on brain-stem audiometry, and electronystagmography showed no spontaneous nystagmus. A bithermal caloric test including stimulation with ice water elicited no vestibular responses on either side.

Fig. 3 Pure-tone audiometry before treatment.

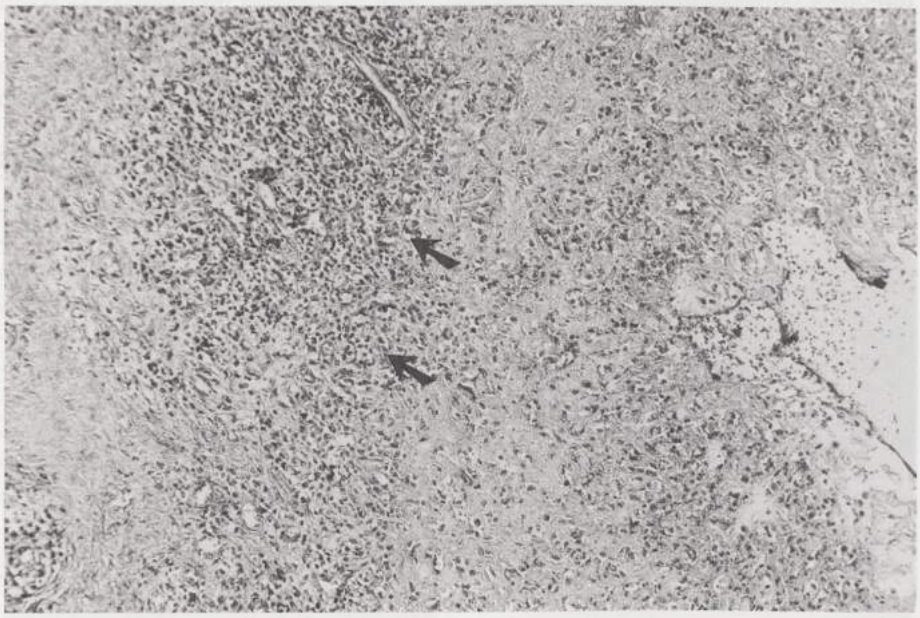


O: air conduction right ear; X: air conduction left ear. Δ: air conduction right ear with masking; <: bone conduction right ear; >: bone conduction left ear.

Routine laboratory examination showed no abnormalities except for an increased sedimentation rate of 112 mm/h. Immunoglobulin levels and complement factors were within normal ranges. Autoantibodies including, anti-neutrophil cytoplasmic antibodies, antiperinuclear antibodies, and rheumatoid factor were negative, whereas the test for antinuclear antibodies was weakly positive. Extensive screening for bacterial and viral infections as well as serological investigations for syphilis and Lyme disease were negative.
Radiological examinations of the chest and joints were normal. Computed tomography (CT) of the brain, petrosal bone, larynx and thorax demonstrated no abnormalities. Magnetic resonance imaging of the petrosal bone and the larynx was normal.

A biopsy of the auricular cartilage showed histopathological changes characteristic of relapsing polychondritis (Fig. 4). A loss of basophilic staining in the cartilage matrix was observed, with infiltration of neutrophils and eosinophils in the perichondral tissue. Locally the destroyed cartilage was replaced by fibrous tissue. Light microscopical and histochemical examination of skin, fascia, and muscle biopsies did not show signs of systemic vasculitis.

Fig. 4 Histopathology of auricular biopsy showing perichondral infiltrate (arrow) and destruction of cartilage (H & E stain; × 100).



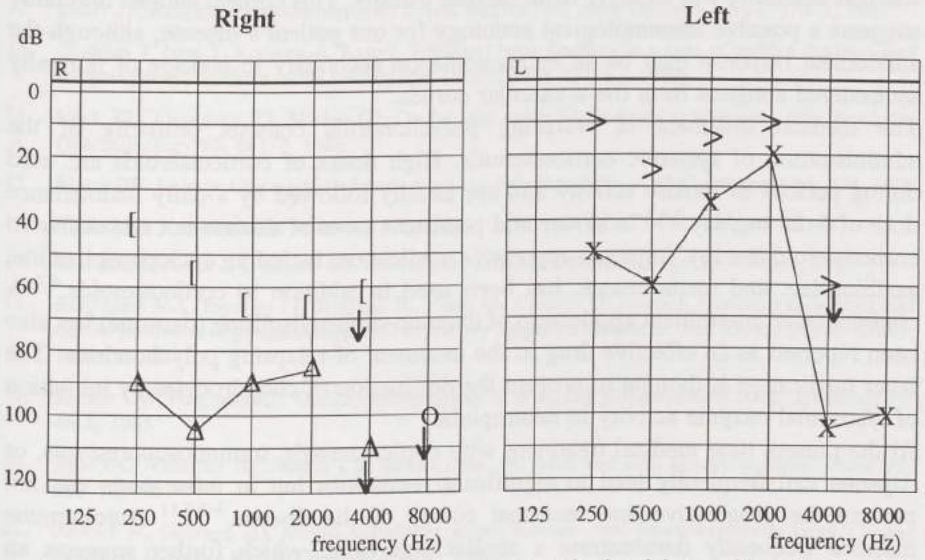
In view of the histopathological findings, the patient's serum antibodies were studied, using the serum of a healthy volunteer as control. The control subject had no otological or ophthalmological medical history, did not wear contact lenses, and did not work in airconditioned spaces. The circulating antibodies against corneal epithelium were assayed by an indirect immunofluorescence technique on bovine cornea.[15,17,30] Sections were scored blindly by two separate investigators using the following classification: strongly positive, positive, weakly positive, and negative. In these studies, the immunofluorescent tests were found to be positive.

The patient was treated intermittently for 4 weeks with high doses of systemic corticosteroids and cyclophosphamide. Subsequently, corticosteroid therapy was continued at a maintenance dose of 30 mg prednisone daily. The general condition of the patient improved significantly, resulting in stabilization of auricular and septal chondritis and respiratory distress.

Additionally, considerable improvement was noted in hearing of the left ear, whereas no change occurred in the complete hearing loss of the right ear (Fig. 5). A hearing aid was placed in the left ear, providing satisfactory rehabilitation of the residual hearing impairment.

Immunofluorescent testing for circulating antibodies against corneal epithelium was repeated 4 weeks after therapy and was found to be weakly positive. After 8 weeks follow-up testing was negative. No circulating antibodies were demonstrable in the control serum.

Fig. 5 Pure-tone audiometry after treatment.



O: air conduction right ear; X: air conduction left ear. Δ: air conduction right ear with masking; <: bone conduction right ear; >: bone conduction left ear.

Discussion

The aetiology of relapsing polychondritis is still unknown, although a possible association has been reported with rheumatic or autoimmune diseases.[3,4,7,8] In 30% of their patients McAdam et al.[7] reported a preceding or coexistent rheumatic or autoimmune disease such as rheumatoid arthritis, polyarteritis nodosa, systemic lupus erythematosus, scleroderma, thyroid disease, Sjögren's disease, glomerulonephritis, or ulcerative colitis. Vasculitic syndromes such as Wegener's granulomatosis and polyarteritis nodosa have also been described in 11-56% of patients with relapsing polychondritis.[16]

Autoantibodies to cartilage and type-II collagen have been demonstrated in the majority of cases of relapsing polychondritis.[5,25-28] Cellular immunity against cartilage mucopolysaccharides has also been observed in the active periods of

relapsing polychondritis.[29] Furthermore, the data indicate possible immunological mechanisms operative in the disease.

Involvement of the eye has been reported in 51-72% of the cases of relapsing polychondritis.[7,8,14] The major ocular manifestations include proptosis, chemosis, episcleritis, scleritis, uveitis, conjunctivitis, keratitis, and peripheral thinning of the cornea.[14,17] Corneal thinning disorders have also been found in Wegener's granulomatosis, polyarteritis nodosa, systemic lupus erythematosus, and rheumatoid arthritis.[22] The presence of corneal epithelium antibodies in systemic diseases with the corneal melting syndrome has been described in several studies.[21-24,30] Circulating antibodies to corneal epithelium were found in our case before treatment, whereas reactivity was strongly reduced after therapy. This corneal antigen immunity suggests a possible immunological aetiology for our patient's disease, although the anticorneal response may be an epiphenomenon secondary to leakage of normally sequestered antigens from the a-vascular cornea.

The medical treatment of relapsing polychondritis consists primarily of the administration of systemic corticosteroids. High doses of corticosteroids are used during periods of intense activity and are usually followed by a daily maintenance dose of 5-25 mg/day.[3,4,7] In severe and persistent cases of disease not responsive to corticosteroid therapy, immunosuppressive medication, including cyclophosphamide, azathioprine, and methotrexate, has been used in addition to corticosteroids.[4,7] A continuous or intermittent application of diamino-diphenylsulfone (dapsone) has also been reported as an effective drug in the treatment of relapsing polychondritis. The latter medication is thought to prevent the destruction of chondrocytes by inhibition of lysosomal enzyme activity in neutrophils.[3,4]

At the present time medical treatment with corticosteroids, immunosuppressants, or dapsone can frequently lead to significant remissions but in most cases can not prevent the progressive and recurrent course of the disease.[3-5,7,11] Autoimmune diseases frequently demonstrate a similar behaviour, which further suggests an autoimmune mechanism in the pathogenesis of relapsing polychondritis. Further studies will be needed to define this association.

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CHAPTER 8

CLINICAL RELEVANCE OF MAGNETIC RESONANCE IMAGING AND COMPUTED TOMOGRAPHY IN COGAN'S SYNDROME

1- Introduction
2- Material and methods
3- Results
4- Discussion

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Introduction

In 1945, the ophthalmologist David Cogan was the first to describe a syndrome of "non-syphilitic deep interstitial keratitis with vestibuloauditory symptoms."[1,2] This disorder is currently known as Cogan's syndrome (CS). More recent reports on this syndrome have shown involvement not only of the eye and ear, but also of other organ systems.[3-6] In a limited number of cases, systemic vasculitis has been associated with CS.[3,5,7]

Despite the clinical evaluation in a large number of individual patients, temporal bone pathology of CS has been described in only 4 cases.[3,8,9,10] In 2 of them (Wolff et al.[9] and Zechner[10]), the clinical symptoms were not in agreement with the diagnostic criteria formulated by Cogan[1] and Norton and Cogan,[2] and they can therefore not be regarded as patients with CS. Wolff et al.[9] described a case with bilateral sensorineural hearing loss, pigment changes in the eyelashes, conjunctivitis, uveitis and hair loss, but without the typical keratitis. The differential diagnosis of the Vogt-Koyanagi-Harada syndrome was suggested. The patient reported by Zechner [10] demonstrated a hearing loss in early childhood and did not suffer from keratitis.

Therefore, the case reports of Fisher et al.[3] and Rarey et al.[8] have been the only autopsy case reports of CS. Both patients had a bilateral interstitial keratitis, total bilateral deafness and suffered from vertigo with vegetative reactions. The case report of Fisher et al.[3] concerns typical Cogan's syndrome (TCS) and because Rarey et al. described an uveitis and episcleritis this case report was defined as atypical Cogan's syndrome (ACS), as formulated in Chapter 2.

Fisher et al.[3] described hypertrophy of the membranous lining of the cochlea, semicircular canals, utricle and saccule, without new bone formation. The scala media of the cochlea, the semicircular canals, and the perilymphatic spaces of the semicircular canals contained a dense acidophilic coagulum. In the case of Rarey et al.,[8] osteogenesis was observed without connective tissue within the membranes of the labyrinth. They found complete ossification of the apical cochlear turns, whereas in the basal part of the cochlea only the scala tympani was patent. Ectopic bone formation was seen in all three semicircular canals, but did not completely obliterate any of the canals. In both cases the middle ears were unremarkable.

Until recently CT scanning was the method of choice in the investigation of bony structures of the inner ear. With the advent of magnetic resonance imaging (MRI) it has become possible to image even soft-tissue structures in the membranous labyrinth. T1- and T2-weighted sequences and a 3-dimensional MR imaging technique with 1 mm slices allow very detailed imaging of the inner ear structures. With gadolinium-enhanced T1-images it is possible to show enhancement of the labyrinth and detect a possible interruption of the "blood-labyrinth barrier," which can indicate an active process. By the simultaneous use of MRI and CT scan, calcified and noncalcified obliterations can be differentiated in the inner ear.

In this study, the vestibular and cochlear labyrinths of 2 TCS and 3 ACS patients (10 ears) were examined by a special MRI technique and high-resolution CT. An attempt

was made to correlate these results with the clinical findings from audiometry and vestibular examination.

Material and methods

Table 1. Main symptoms and signs in five patients with Cogan's syndrome.

PATIENTS	1	2	3	4	5
MAIN AUDIOVESTIBULAR FINDINGS					
Symptoms:					
- tinnitus	+	+	+	+	+
- fullness in the ears	+	–	+	+	–
- vertigo	+	+	+	+	+
- vegetative reactions	+	+	+	+	+
Signs:					
- sensorineural hearing loss	+	+	+	+	+
- response to caloric stimulation	+	–	–	–	–
MAIN OPHTHALMOLOGICAL FINDINGS					
Symptoms:					
- eye discomfort	+	+	+	+	+
- photophobia	+	+	+	+	+
- redness	+	+	+	+	+
Signs:					
- interstitial keratitis	+	+	+	+	+
- hyperaemic perilimbal vessels	+	–			
- conjunctival hyperaemia	+	+	+	+	+
- uveitis		+	+		
- episcleritis		+			+
- scleritis			+		
- cells anterior chamber			+		
- excess of lacrimation	+	+	+	+	+
- fundus	–	–	–	–	–
MAIN SYSTEMIC FINDINGS					
Symptoms:					
- general illness	+	+	+	+	+
- fatigue	+	+	+	+	+
- arthralgia	+		+		
- myalgia		+			
- testicular pain	+			+	

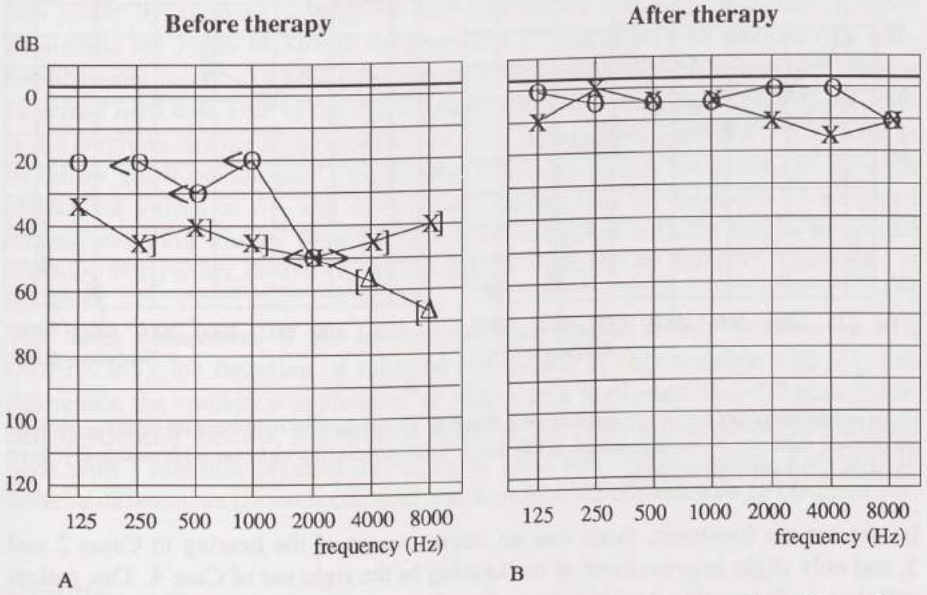
Symptoms and signs, are present: +; not present: –

Patients. Five patients (1 woman, 4 men; median age 22.5 years) with the clinical characteristics of CS were examined. All patients had a bilateral sensorineural hearing loss with tinnitus and vertigo with vegetative reactions. They all suffered from pain, photophobia and redness of the eyes, and general illness with fatigue. In all cases, interstitial keratitis and conjunctival hyperaemia were seen. For further

details about symptoms and signs, see Table 1. We defined patients 1 and 4 as TCS and patients 2, 3 and 5 as ACS, because of the uveitis, scleritis and episcleritis seen in these patients (for a definition of TCS and ACS see Chapter 2). Routine neurological and otorhinolaryngological examination revealed no abnormalities.

In addition to the physical examination, all patients were repeatedly submitted to audiovestibular investigations. Laboratory findings and specific immunological tests of serum and cerebrospinal fluid showed no relevant abnormalities except an increased erythrocyte sedimentation rate (ESR), leukocytosis in all patients, and a white blood cell count of 29/mm^3 in the cerebrospinal fluid in Case 1. In Cases 1 and 2 the presence of circulating corneal antibodies could be established. In both cases, corneal antibodies were found at the beginning or during exacerbation of the syndrome.[6] Serological tests for syphilis were negative. Complete bacterial or viral screening of serum and cerebrospinal fluid revealed a herpes simplex virus titer elevation in serum in case 1 only. Multiple biopsies did not show any signs of vasculitis. On radiographic examination, no abnormalities were observed (sinuses, thorax, polytomography and abdomen).

Fig. 1 Case 1: (A) before therapy; (B) after therapy.

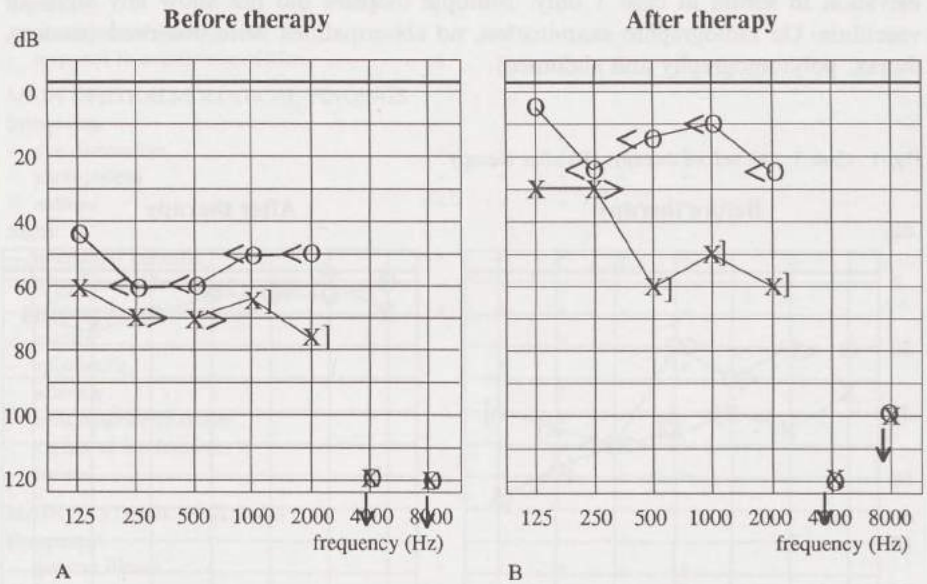


O: air conduction right ear; X: air conduction left ear. Δ: air conduction right ear with masking; <: bone conduction right ear; >: bone conduction left ear; [: bone conduction right ear with masking;]: bone conduction left ear with masking.

All patients were treated with high dosages of prednisone (1 mg/kg daily), and if there was no response after 2 weeks with supplementary cyclophosphamide or azathioprine. Case 1, who had a slightly sloping sensorineural hearing loss of 35 dB for the right ear and 45 dB for the left ear, recovered completely after treatment with high-dosage prednisone, with normal hearing and without general complaints (Fig. 1A and B).

The hearing of Case 5 improved after treatment with a high dosage of corticosteroids (80 mg prednisone daily) and azathioprine (3 × 50 mg, daily), initially in the right ear (± 40 dB) and later followed by a slight improvement at the lower tones of the left ear (Fig. 2A and B).

Fig. 2 Case 5: (A) before therapy; (B) after therapy.



O: air conduction right ear; X: air conduction left ear. Δ: air conduction right ear with masking; <: bone conduction right ear; >: bone conduction left ear; [: bone conduction right ear with masking;]: bone conduction left ear with masking.

In spite of the treatment, there was no improvement of the hearing in Cases 2 and 3, and only slight improvement of the hearing in the right ear of Case 4. This patient still has a fluctuating hearing loss. In all cases, the keratitis was cured with dexamethasone eye drops, the general condition stabilized and the postural instability persisted.

Magnetic resonance imaging and computed tomography. In all patients, both temporal bones were examined by MRI and CT.

MRI was performed on a 1.0-Tesla active shielded magnet (Siemens, Magnetom SP 42, Erlangen Germany) including 3-mm contiguous axial unenhanced and Gd(gadolinium)-DOTA-enhanced (Dotarem, Guerbet Laboratories, France) T1-weighted 2D spin echo images, 500/15/4 (TR/TE/excitations), 4-mm axial T2-weighted 2D spin-echo images, 2500/15, 90/1 with a 0.8 mm gap and 1-mm-thin contiguous axial CISS-3DFT (Constructive Interference in Steady State 3-Dimensional Fourier Transformation) images. The total acquisition time was 8 min and 32 s for the T1- and 10 min 40 s for the T2-weighted images, and 5 min and 32 s for the CISS images.

The CISS sequence scheme, providing the CISS images, is a 3DFT sequence scheme using the steady-state free procession of spins. In this sequence scheme a "true" fast imaging with steady procession (FISP) sequence is run once with alternating and once with non-alternating radiofrequency pulses, in order to shift the dark bands caused by very small magnetic-field inhomogenities and local field distortions attributable to susceptibility changes that are normally produced by the patient. The images produced by the addition of the corresponding images of the two three-dimensional data sets, have a homogeneous intensity distribution over the whole image and very good contrast between the high-signal intralabyrinthine fluid and the low signal of the surrounding bony labyrinth. A 3-D reconstruction of the inner ear was made by applying a targeted MIP (maximum intensity projection). Used parameters are 1 slab of 32-mm thickness and 32 partitions with sections of 1-mm. Simultaneous imaging of both inner ears was possible by the application of a circular polarized head coil. Due to the thin adjacent slices, the very high signal of the fluid in the labyrinth and the high resolution of the 3-dimensional sequence it was possible to follow small pathological labyrinthine structures within the inner ear. In each patient, the values of T1- and T2-weighted images and Gd-enhanced T1-weighted images and CISS images were evaluated and compared with the results in normal controls. For further details of the used MRI methods we refer to Casselman et al.[11,12]

Soft tissue obliteration of the labyrinthine fluid spaces is only possible on MR (3DFT-CISS), but detection of calcified obliteration is only possible with CT. For this reason the combined application of MRI and a high-resolution CT scan (9800 Hilight, General Electric, Milwaukee, Wisc) of the petrous portion of the temporal bone with 1-mm-thin adjacent slices, in an axial and coronal plane, was used in order to differentiate between calcified and noncalcified obliterations in the inner ear.

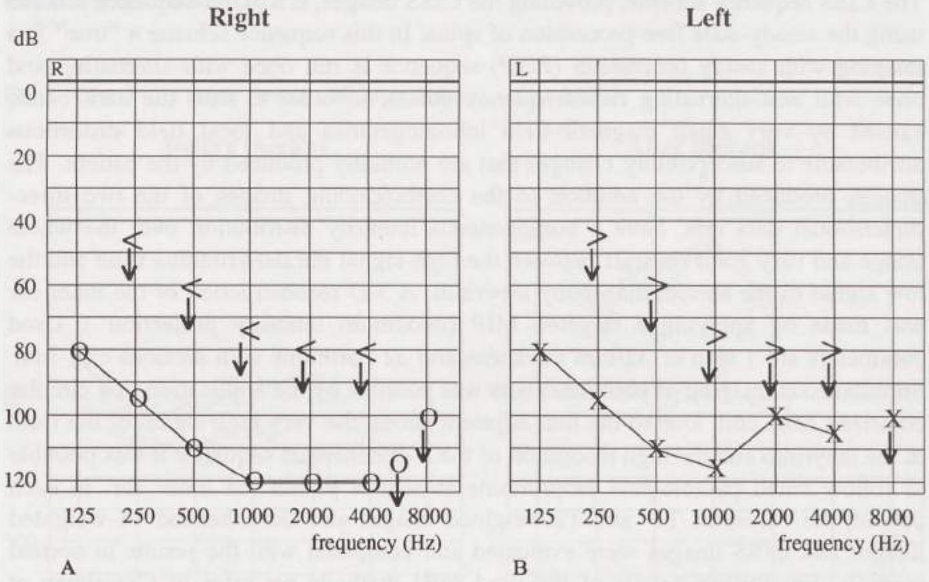
Results

Case 1 had a slightly sloping sensorineural hearing loss of 35 dB for the right ear and of 45 dB for the left ear (Fig. 1A). After treatment, his hearing recovered completely (Fig. 1B). On caloric examination, both labyrinths responded normally and symmetrically.

T1- and T2-weighted spin echo images and CISS-3DFT images showed normal membranous labyrinths. A gadolinium-enhanced T1-weighted sequence did not show enhancement of the inner ear. The CT scan was normal.

Case 2 showed a flat sensorineural hearing loss of about 115 dB on the right and 110 dB on the left side (Fig. 3). Electronystagmography showed no response to caloric stimulation.

Fig. 3 Case 2. Pure tone audiometry.



O: air conduction right ear; X: air conduction left ear. <: bone conduction right ear; >: bone conduction left ear.

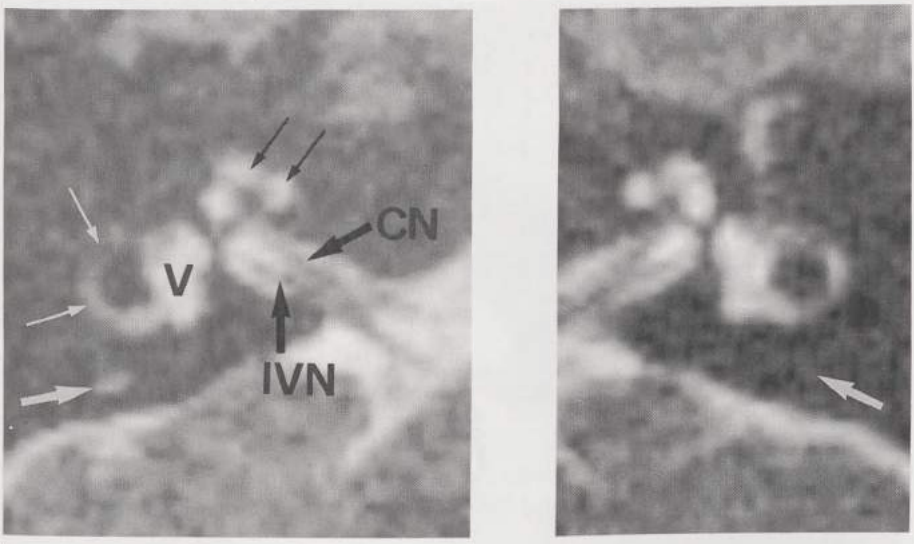
T1- and T2-weighted spin echo images and CISS-3DFT images showed a normal membranous labyrinth in the right inner ear (Fig. 4A), except for a narrowing of the posterior semicircular canal in the region of the crus commune, seen on the CISS-3DFT images. In the left ear, the superior and the posterior semicircular canals were completely obliterated on the CISS-3DFT images (Fig. 4B). T1- and T2-weighted images did not show the pathology.

The images of the cochlea were normal. A gadolinium-enhanced T1-weighted sequence did not show enhancement of the inner ear. The CT scan revealed no abnormalities, indicating that the obliterations observed in the inner ears were due to soft tissue accumulations.

Fig. 4 1-mm-thin axial 3D-CISS-MR image through the right (A) and left (B) labyrinth at the level of the lateral semicircular canal.

A: Normal high-signal intensity intralabyrinthine fluid can be seen in the cochlea (long thin black arrows), vestibule (V), lateral semicircular canal (long thin white arrows) and posterior semicircular canal (large white arrow). The intralabyrinthine fluid is iso-intense with the CSF around the cochlear nerve (CN) and inferior vestibular nerve (IVN) inside the internal auditory canal.

B: The high-signal intensity fluid inside the posterior semicircular canal is lost (large white arrow). On the corresponding CT image no calcifications were seen inside the posterior semicircular canal. Consequently the obliteration must be caused by soft tissue inside the membranous labyrinth.



A B

Case 3 was completely deaf in both ears. Electronystagmography showed no response to caloric stimuli.

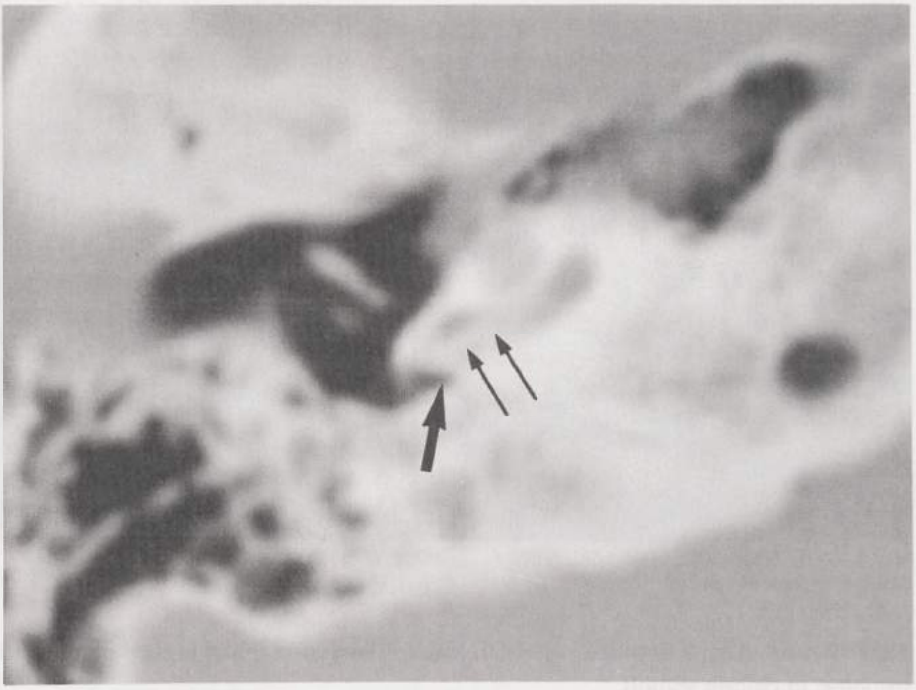
CISS-3DFT images of the right ear showed complete obliteration of the superior and posterior semicircular canals whereas only parts of the ampula and the crus commune could be visualized. The lateral semicircular canal of the right inner ear was narrowed over the whole length and interrupted in its most lateral part.

On the left side, the lateral semicircular canal was narrowed, and we found obliteration of the posterior part and the anterior part of the superior semicircular canal. The posterior semicircular canal was completely obliterated with the exception of the caudal part. Unenhanced T1- and T2-weighted images were normal.

The obliterations of the lateral semicircular canal in both labyrinths were stronger on the CISS-3DFT images compared to the images on CT scan, suggesting an obliteration by bony and soft tissue.

Depositions of pathologic tissue were seen in the right and left vestibulum and cochlea. On the CT scan, we observed calcifications in the basal turn of both cochleas (Fig. 5). On the right side the second and apical turn were completely obliterated and on the left side partially obstructed by soft tissue.

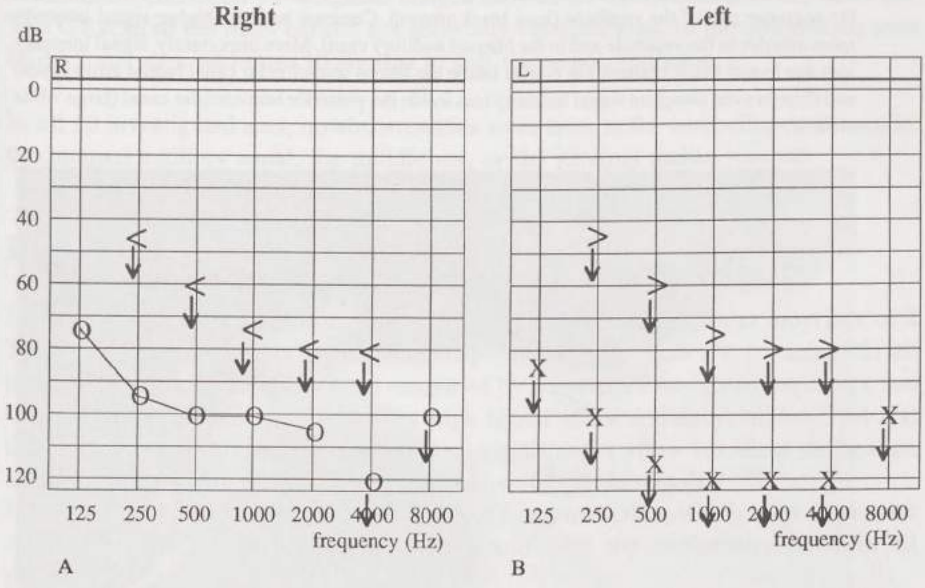
Fig. 5 Axial CT image through the right labyrinth at the level of the basal turn of the cochlea. The low-density fluid inside the basal turn of the cochlea is replaced by high-density calcification (long thin black arrows) in the posterior part of the basal turn near the round window niche (large black arrow)



Gadolinium-enhanced T1-weighted images showed a distinct enhancement of the cochlea and vestibulum on the right side and slight enhancement on the left side.

Case 4 developed a sensorineural hearing loss of 100 dB in the right ear and total deafness on the left side (Fig. 6). Electronystagmography showed no response to caloric stimuli on either side.

Fig. 6 Case 4. Pure tone audiometry.



O: air conduction right ear; X: air conduction left ear. <: bone conduction right ear; >: bone conduction left ear.

CISS-3DFT images showed complete obliteration of the superior and posterior semicircular canals, and narrowing of the lateral part of the lateral semicircular canal of the right inner ear.
On the left side, obstruction of the superior semicircular canal was found, with obliteration of the lateral and posterior semicircular canals (Fig. 7).

Soft tissue was found in the posterior part of the basal turn, and in the caudal part of the second turn of the right cochlea. On the left side, the narrowing of the basal and second turn of the cochlea was more prominent (Fig. 7). The T1- and T2-weighted sequences did not reveal the pathology, and a gadolinium-enhanced T1-weighted sequence did not show enhancement of the inner ear.
The CT scan of the inner ear did not show any calcifications, so the obliterations found in the inner ears must be due to soft tissue accumulation.

Fig. 7 Axial 1-mm-thin 3D-CISS-MR image through the left cochlea and vestibule. Slight loss of high-signal intensity is seen in the center of the basal turn of the cochlea (black arrowheads) and in the posterior part of the vestibule (long black arrows). Compare with the higher-signal intensity more anterior in the vestibule and in the internal auditory canal. More importantly, signal intensity loss due to soft tissue obliteration is seen inside the lateral semicircular canal (white arrowheads) and there is even complete signal intensity loss inside the posterior semicircular canal (large white arrow).

Case 5 developed a flat sensorineural hearing loss of 55 dB on the right side and of 70 dB on the left side with total deafness at higher frequencies (Fig. 2A). After treatment with a high dosage of corticosteroids (80 mg prednisone daily) and azathioprine (3 × 50 mg, daily), his hearing improved in the right ear to a 15-dB loss, and there was slight improvement at the lower frequencies in the left ear (Fig. 2B).

Electronystagmography showed no response to caloric stimuli on the left side and a hypofunction on the right side. There was a slight spontaneous nystagmus to the right side.

CISS-3DFT images showed obliteration of the superior and posterior semicircular canals of the left inner ear. The superior semicircular canal on the right side was narrow; the lateral and the posterior semicircular canals were normal.

Slight obliterations were found in the anterior part of the left vestibulum. The images of the posterior part of the basal turn of the left cochlea were indicative of a

deposition of soft tissue. On the right side, the cochlea and vestibulum were normal. Gadolinium-enhanced T1-weighted images showed no enhancement of the inner ear. The CT scan of the inner ear did not show any calcifications, so the obliteration seen in the inner ears was most likely due to soft tissue accumulation.

In all 10 investigated ears, no abnormalities were seen in the cerebellopontine angle, the internal auditory canal, the middle ear, or the external auditory canal.

Discussion

In this study, the pathological changes in the cochlea and vestibular labyrinth of 2 TCS and 3 ACS patients were studied by MR imaging and CT scanning. In all patients, both temporal bones were examined by T1- and T2-weighted sequences and CISS-3DFT. The thin slices, the very high signal of the intralabyrinthine fluid and the high spatial resolution of the 3-dimensional images allow excellent delineation of small normal and pathological structures within the labyrinth.

MRI and CT scans of all 10 middle ears were unremarkable, which is in agreement with the findings reported in autopsies[3,8] and with the audiometry done in all patients.

In Case 1, who recovered completely with normal hearing, we found normal labyrinths. In the remaining 4 cases, narrowing or obliteration of parts of the superior, lateral and posterior semicircular canals was seen. Soft tissue inside the vestibulum was found in 3 labyrinths. This is in agreement with the clinical findings as all 4 patients were suffering from vertigo with vegetative reactions. The electronystagmograms showed no response to caloric stimuli in 7 labyrinths and a hypofunction in one ear.

In 3 patients, we found aberrations in the cochlea consistent with the audiometry done at the time of MR and CT investigations. In Case 3, who is completely deaf, both cochleas were completely obliterated with soft and bony tissues. Compared to the total hearing loss in the left ear, and the residual hearing at the low and middle frequencies of the right ear in Case 4, soft tissue was visible in the basal and second turns of the right cochlea, and more prominent in the basal and second turns on the left side. In Case 5, hearing improved considerably after treatment in the right ear but only slightly at the lower frequencies on the left side. A high-frequency loss persisted on both sides. In this case, the images of the posterior part of the basal turn of the left cochlea indicated accumulation of soft tissue, correlating with the high-frequency hearing loss, while on the right side no pathology was seen in the cochlea. No obliterations were observed in the cochleas of Case 2, who is known to have had the syndrome for 4 years, with total deafness on one side, and subtotal deafness on the other side side. We have no explanation for these negative findings.

The obliterations by soft tissue showed in these cases resemble the findings described in the autopsy reports in the literature. Fisher et al.[3] noticed a slightly thicker membranous lining of the cochlea and semicircular canals. The endolymph-

atic duct of the cochlea, the semicircular canals, and the perilymphatic spaces of the semicircular canals contained soft tissue. In agreement with Rarey et al.[8], who found osteogenesis in the inner ear, we found calcifications of the membranous labyrinth discovered on CT scanning in Case 3. It was suggested by Rarey et al.[8], that the osteogenesis in the inner ear represents a more advanced inner ear pathology. Rarey's patient died 33 years after the onset of the syndrome and Fisher's 4 years after. This hypothesis is not corroborated by our findings of new bone formation in Case 3, who was known to have had the syndrome for hardly more than 2 years.

With gadolinium-enhanced T1-weighted images we found enhancement of the cochlea and vestibulum on both sides in Case 3, probably indicating an active process, such as vasculitis or infection, with interruption of the "blood-labyrinth barrier." This patient developed a rapidly progressive hearing loss resulting in almost immediate deafness on both sides. Except for her deafness, she was completely healthy at the time the MRI was made. There were no signs of infection, vasculitis or recurrence of the disease at that time.

The aetiology of CS is still unknown. The differential diagnosis of this syndrome includes systemic diseases and vasculitic syndromes such as polyarteritis nodosa and relapsing polychondritis.[5,7] These diseases are less frequently associated with eye and audiovestibular involvement. On the other hand analogous findings such as obliterations of soft tissue and bone of the inner ears have also been described in polyarteritis nodosa and relapsing polychondritis.[13] Moreover, Kimura and Perlman[14] have shown osteogenesis and fibrous tissue after arterial obstruction in guinea pigs, implying that the inner ear pathology in these syndromes is probably caused by obstructive vasculitis of the labyrinthine artery or its branches.

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CHAPTER 9

GENERAL DISCUSSION AND SUMMARY

1- Introduction
2- Defining Cogan's syndrome
3- Results
4- Therapy
5- Aetiopathological considerations
6- Conclusions
7- Recommendations

Introduction

In 1945, Cogan reported four cases of "nonsyphilitic interstitial keratitis associated with vertigo, tinnitus, or hearing loss." In 1949 he added four more cases. Since then this condition has become known as Cogan's syndrome (CS). Up till now some 187 cases have been published.
Because of the great variety of symptoms, some authors distinguish between typical (TCS) and atypical Cogan's syndrome (ACS). Typical Cogan's syndrome is defined by Cogan's original criteria. Atypical Cogan's syndrome is defined as a condition with audiovestibular manifestations, with or without corneal involvement and other ocular findings.[3-5]
More recent reports have indicated involvement of other organ systems and of systemic vasculitis.[2,6-8] The latter may possibly be associated with an immunological disturbance.[3,9,10] Nevertheless, the cause of CS is still obscure.

Defining cogan's syndrome

Interstitial keratitis and sensorineural hearing loss are the essential clinical features of CS. Both symptoms are also frequently expressed by other systemic diseases. Chapter 2 gives an overview of the differential diagnosis between CS and other diseases on the basis of the eye and ear symptoms.
In order to define CS, we have used Cogan's original criteria. We did make some modifications, however, to facilitate the differential diagnosis. The most important adaptions are the precise localizations of the opacities in interstitial keratitis and the exacerbations and remissions of the eye complaints. Furthermore, we differentiate between conjunctivitis and conjunctival hyperaemia, as well as between vertigo and vestibular disturbance.
Based on a review of the literature, Chapter 2 presents new working definitions of TCS and ACS:

Typical Cogan's syndrome (TCS):
bilateral focal, peripheral interstitial keratitis with or without conjunctival hyperaemia or ciliary flush; often with typical exacerbations and remissions; associated with usually bilateral fluctuating sensorineural hearing loss, tinnitus, and vestibular disturbance; with or without systemic manifestations of unknown origin; without a history of eye or ear disorders preceding the onset of the syndrome.
Atypical Cogan's syndrome (ACS):
the above-described syndrome combined with another significant inflammatory eye lesion in addition to interstitial keratitis.

The term *nonsyphilitic* interstitial keratitis, introduced by Cogan, is obsolete. Although the ophthalmological lesions in CS and syphilis show no gross differences,

both diseases can be easily differentiated by their clinical manifestations and by serology (Chapter 2).

Results

CLINICAL FINDINGS

In a retrospective study (Chapters 4 and 5), we have investigated the clinical data of 98 patients presumed to suffer from CS. They were treated in 10 different West European countries between 1968 and 1993. According to our criteria 37 of them were diagnosed as TCS and 22 as ACS. This is the largest group of CS patients ever studied.

Ophthalmological findings

Bilateral interstitial keratitis was present in 56 patients. In only 2 TCS and 1 ACS patients keratitis was unilateral. The localization and appearance of corneal opacities were described in only half of the cases (Chapter 4). This is unfortunate because of its central role in the differential diagnosis of CS. Exacerbations and remissions of eye complaints were very common, although not always observed. One explanation might be early successful treatment with glucocorticoids. Moreover, ophthalmological symptoms may be of minor importance in very ill patients.

Otological findings

a) General

In all TCS and ACS patients a sensorineural hearing loss was found, mostly at the same time in both ears. If started unilaterally, the hearing loss in the other ear developed within days. Eventually, except for 1 ACS patient, all developed bilateral sensorineural hearing loss.

The sensorineural hearing loss is localized in the cochlea. Recruitment tests were positive in most cases. Per-stimulatory adaptation tests were always negative, and BERA showed no signs of retrocochlear involvement. The labyrinthine localization of CS was confirmed by CT- and MR-imaging studies (Chapter 8).

Tinnitus was present in a high percentage (84%) of patients. This is in accordance with the literature.[3,4,6] Patients mentioned fullness in the ears (32% TCS and 33% ACS). An endolymphatic hydrops might be responsible for this phenomenon.[11-13]

b) Cut-off frequency

A cut-off frequency in the audiogram was seen exclusively between 1000 and 2000 Hz, the latter frequency being the most common localization of this phenomenon. This finding is not mentioned in the literature, but in some reports audiograms show similar curves.[14-17] Cut-off frequencies have also been reported in other cochlear lesions, such as progressive hereditary deafness and ototoxicity.[18,19] Apparently there is a major difference in the physiology of the low-tone and high-tone part of the

cochlea. As suggested in earlier reports, two systems can be distinguished in the cochlea: one for the lower frequencies, the other for the higher frequencies. Futhermore, experimentally induced endolymphatic hydrops in the guinea pig demonstrates a similar 'cut-off frequency'.[20]

c) Fluctuations in hearing
Sensorineural hearing loss was found to fluctuate in the majority of cases. In some patients, these fluctuations occurred spontaneously. In most cases they were seen during therapy and related to treatment. Fluctuations were seen irrespective of the degree of hearing loss. Nonetheless, patients with slight and moderate losses generally demonstrated greater fluctuations than those with severe losses.

d) Low-tone hearing fluctuations
Fluctuations in hearing were particularly seen at lower frequencies. When we relate this finding to the observations: (1) that low-tone hearing loss is seen in particular in the early stages of the disease, (2) that many patients complain of fullness in the ears, and (3) that endolymphatic hydrops is found in temporal bone pathology studies of patients with CS, it seems likely that endolymphatic hydrops plays a role in Cogan's syndrome.

e) High-tone hearing fluctuations
High-tone hearing fluctuations were seen to a lesser extent than low-tone fluctuations. They mostly occurred in ears with slight and moderate losses.
Irreversible high-tone hearing loss was ultimately observed in 96% of the TCS and 80% of the ACS patients. We presume that high-tone loss in CS is the result of irreversible hair cell loss.[18,21]

f) Conductive hearing loss
In five TCS cases, a small degree of conductive hearing loss was found superimposed on the sensorineural hearing loss. In some patients a slight decrease of middle ear compliance was measured at the same time. Stapedial reflexes were not measured in these patients.
Some authors have reported a mixed hearing loss in Cogan's syndrome.[22,23] Because of the decreased compliance, Djupesland et al.[23] postulated that the conductive loss might be due to stapes fixation. If osteoneogenesis in the labyrinth represents a more advanced inner ear pathology in CS, and new bone formation is located in the vicinity of the oval window, stapes fixation might be imaginable.

g) Effect of treatment in relation to degree of hearing loss
Improvement or restoration of hearing was only seen in ears with an initial loss of less than 60 dB. In patients with an initial hearing loss of more than 60 dB hearing deteriorated in spite of therapy. This may be explained by the fact that all outer hair cells are degenerated which accounts for a loss of about 60 dB (provided that the majority of inner hair cells is still intact).[18,21]

Vestibular findings

Vertigo was the most common complaint (89% TCS and 95% ACS). The remaining patients suffered from dysbalance, which is in accordance with the literature.[24]

A caloric test was performed in almost all patients. No caloric function in both ears was found in 66% of the TCS and 62% of the ACS patients. Only 4 TCS and 3 ACS patients showed a normal caloric test. In 3 out of these 4 TCS patients, a spontaneous nystagmus was found. Only 1 TCS and 3 ACS patients showed no aberrations in their vestibular tests.

All patients with initial no caloric response complained of a persisting postural instability at stationary phase. They suffered from balance disorders, especially in the dark and after fast head movements. Only in a few patients these complaints were confirmed by caloric testing.

In 3/8 TCS and 1/5 ACS patients with bilateral hypofunction or unilateral dysfunction the vestibular apparatus demonstrated compensation in the rotating chair test.

McDonald et al.[24] noted that 11 out of 18 (61%) patients had no vestibular function upon caloric testing. In their study, 5 patients remained stable with diminished vestibular function.

General findings

Most patients in our study were young (average age 25 years). The disease often started with vague general symptoms. Then, within some days or weeks, they developed keratitis, sensorineural hearing loss, tinnitus, and dysbalance with nausea and vomiting. This was frequently accompanied by nonspecific findings, such as: fever, weight loss, fatigue, head-and-neck discomfort, commonly accompanied by arthralgia, myalgia, and abdominal discomfort.

An upper respiratory tract infection preceded the onset of CS in 43% of the TCS and 27% of the ACS patients. Attempts to isolate and identify a micro-organism at the time of onset of CS were only occasionally successful (Chapter 4).

One remarkable nonspecific finding is testicular pain. This was observed in 2/4 male patients seen by the author himself. A testicular biopsy taken from one of them revealed no abnormalities, and notably no vasculitis. Apart from our 2 cases, this complaint was recorded only once in the group of 28 male patients. Probably this kind of pain is a minor detail in very ill patients and may easily be overlooked. All 3 patients had TCS.

In our retrospective investigation, histopathological study of biopsies of skin, fascia, and muscle did reveal nonspecific abnormalities but no vasculitis (Chapter 4).

It has been suggested that CS is a manifestation of a systemic disorder, e.g. polyarteritis nodosa or relapsing polychondritis.[25,26] Therefore, we present a case of histopathologically confirmed relapsing polychondritis, which is presumed to resemble CS (Chapter 7). In this patient bilateral sensorineural hearing loss, tinnitus, and vertigo, without the usually observed conductive hearing loss was found[27,28] Furthermore, cornea oedema and guttata, ciliary, conjunctival and episcleral hyperaemia were seen in the right eye only. Although there was never any evidence

of an interstitial keratitis, the resemblance to ACS is striking. If the corneal involvement had been interpreted as interstitial keratitis, this case would have been diagnosed as "Relapsing polychondritis: An atypical case of Cogan's syndrome."
In this retrospective study we could not find gross evidence for systemic involvement (Chapter 4). It is possible that the incidence of serious systemic disease was lower in our patient group because they were brought in mostly by otorhinolaryngologists. In contrast the patient groups of Haynes et al.[3] and Vollertsen et al.[6] were enlisted from Departments of Rheumatology and Internal Medicine.

LABORATORY FINDINGS

General

Except for an occasionally-elevated erythrocyte sedimentation rate and leukocytosis, the general laboratory findings were usually normal, both in our study and in the literature. This is interesting in itself, because even in a control group of clinically healthy people, one would expect some idiopathically abnormal laboratory findings. One possible explanation might be that the patients are young and have a blank clinical history.

Immunology

A survey of general immunological parameters was essentially negative (Chapter 4). This is plausible, assuming that only the inner ear and the cornea are involved in an 'inflammatory' process. The slight elevation of the erythrocyte sedimentation rate and of the acute phase proteins, seen in some patients, may be associated with one of these processes or with an underlying infection of unknown nature.
Chapter 6 described autoimmune reactivity against corneal antigens in one TCS and one ACS case. In both patients, corneal autoantibodies were found at the beginning or during an exacerbation of the syndrome and they decreased significantly after glucocorticoid therapy. Autoantibodies were also demonstrated by Arnold et al.[29] They proved not only the presence of antibodies reacting with the cornea but also with healthy inner ear tissue.
We also found corneal autoantibodies in a patient with relapsing polychondritis (Chapter 7). In addition their presence has also been described in Fuchs' heterochromic cyclitis[30] and Mooren's ulcer.[31] So the presence of corneal antibodies appears to be nonspecific to CS.

MAGNETIC RESONANCE IMAGING AND COMPUTED TOMOGRAPHY

In Chapter 8, the pathological changes in the inner ears of 2 TCS and 3 ACS patients were studied by a combined application of MR-imaging and CT-scanning. It was possible to visualize pathological structures in the labyrinth. In one patient, who recovered completely, normal labyrinths were found. In the remaining 4 cases,

narrowing or obliteration of the vestibular labyrinth with soft tissue was seen. This is in agreement with the clinical findings of vertigo with vegetative reactions and absence of caloric response.
In 3 patients, accumulations of soft tissue were seen in the basal or second turn of the cochlea. That finding is consistent with the prominent high-tone hearing loss at the time of MR and CT examination. Apart from soft tissue, bony tissue was observed in the cochlea of Case 3, who was completely deaf.
Gadolinium-enhanced T1 images showed enhancement of the cochlea and vestibulum on both sides in Case 3, indicating an active process, such as vasculitis or inflammation. Almost immediately this patient became deaf on both sides. Except for her deafness, she was completely healthy when the MRI was made. There were no signs of infection, vasculitis, or recurrence of the syndrome at that time.

Therapy

EFFECTS OF GLUCOCORTICOID THERAPY

Ophthalmological symptoms healed in all patients, irrespective whether this treatment was administered systemically, topically or combined. In the majority of cases, the symptoms were cured within 2 weeks.

Improvement of hearing was found in 9/34 TCS and 4/18 ACS patients. Hearing only recovered if the glucocorticoid therapy was started soon after the onset of the syndrome. Hearing improved in all 7 patients (TCS and ACS) treated within one week, and in 2 out of 6 cases treated within 2 weeks (Chapter 5).
All patients who showed hearing improvement, received a systemic glucocorticoid dosage of >1 mg/kg per day. In all patients treated with a dosage of <0.8 mg/kg hearing deteriorated. Haynes et al.[3,32] found improvement of hearing in 10 out of 18 CS patients (55%) treated within the first 2 weeks after the onset of hearing loss.

EFFECTS OF CYTOTOXIC IMMUNOSUPPRESSIVE DRUGS

The role of cytotoxic immunosuppressive drugs such as cyclophosphamide and azathioprine has not been established yet. Because of their serious side effects (haematological toxicity, teratogenicity, suppression of gonadal development), these drugs were never given in the initial phase of the syndrome.
In our clinic 5 patients were treated with azathioprine (2mg/kg; daily) in addition to systemic glucocorticoids. Hearing stabilized in 3 patients and was almost completely restored in one patient.

SPONTANEOUS IMPROVEMENT

Spontaneous improvement of hearing was seen in 2/3 TCS and 2/4 ACS patients. This group of patients is too small to allow conclusions.

Aetiopathological considerations

IMMUNOLOGY

Several authors[3,9,10,29,33] have suggested that an autoimmune process underlies the pathogenesis of CS. It is commonly thought, although without much substantiation, that the trigger of such a process could be an upper respiratory tract infection. This is believed to occur through the induction of an antiviral response cross-reacting with auto-antigens to inner ear, eye, and, occasionally, other organ tissues as well.

If one assumes that the tissue damage in CS is indeed immunologically mediated, the involved mechanism(s) might be discussed using the hypersensitivity classification of Coombs and Gell.[34] It is likely that the type of reaction will be the same in the eyes and ears. In type III hypersensitivity (mediated by circulating immune complexes) multiorgan involvement is frequently observed. Basement membranes (e.g. in the stria vascularis) are predilection sites.[35] One possibility is that a vasculitis is caused by deposition of circulating immune complexes in the vessel walls. Because the cornea is a-vascular with only minimal limbal vascularization, preformed immune complexes do not easily diffuse into the cornea. However, free autoantibodies could penetrate the tissue and initiate inflammation. Another possibility is that the syndrome started from a bacterial or viral infection and inflammation, with corneal vessel ingrowth followed by immunological reactions.
Both the occurrence of type II, the antibody-dependent cytotoxic hypersensitivity, and type IV, (T-) cell mediated hypersensitivity, would imply that the involvement of the eyes and ears in CS might be based on shared auto-antigenic cross-reactivity. These hypersensitivity reactions might be involved either in an immunopathogenic mechanisms or as an epiphenomenon. Some antigens in eyes and ears have been identified, but until now no cross-reactivity has been demonstrated.[29,35-39]

Theoretically, in an autoimmune disease, antibodies or T-lymphocytes reactive with relevant tissue components should be present. In addition, autoreactivity should clearly contribute to tissue damage. The scanty data available at this moment do not provide hard evidence for an autoimmune pathogenesis of CS.
Unfortunately, identification of immunoglobulins, immune-complex depositions, cellular infiltrates, and relevant auto-antigens in otological and ophthalmological disorders is hampered by practical considerations. It is impossible to take a biopsy from the inner ear or the cornea of a living patient. Post-mortem investigation of corneal tissue is possible by using cryotome sections. Immunohistopathological

investigation of the inner ear, however, involves fixation and decalcification, which may interfere with the antigenic properties of tissue components.

EMBRYOLOGY

The question arises whether certain similarities in the embryogenesis of the inner ear and the cornea could account for the simultaneous involvement of both organs in CS. The membranous inner ear develops from the auditory placode which derives from the ectoderm.[40] The stria vascularis also develops from ectoderm but rests on a highly vascularized strip derived from the surrounding mesoderm.[41]
The corneal epithelium itself is of ectodermal origin. The stroma is of mesodermal origin and the endothelium is formed by a layer of flattened mesenchymal cells.[42] Bowman's membrane derives from the stroma, and Descemet's membrane is commonly considered to be derived from the endothelium.[43]
It is noteworthy that the stria vascularis rests on mesoderm and that the corneal stroma completely derives from mesoderm. This is interesting because interstitial keratitis in CS only involves the stroma of the cornea. Assuming that CS is a disorder in which mesenchymal tissue is involved, then the stria vascularis is likely to be affected too.

HISTOPATHOLOGY

A great number of papers have addressed the question, whether CS represents a form of vasculitis. However, up till now, no signs of vasculitis have been found in the biopsies studied.[12,44] In the six cases (3 TCS and 3 ACS) in which the (histo)pathological changes in the eye and ear in CS were studied,[12,13,44-47] no vasculitis was found either.
In the temporal bone pathology studies of CS patients, 3 important pathological findings have been decribed: 1) endolymphatic hydrops, 2) formation of connective tissue, and 3) osteoneogenesis.[12,13,44]
Endolymphatic hydrops is found in various other diseases,[48,49] including polyarteritis nodosa,[50] a condition resembling CS in some respects.
Fibrous tissue ingrowth and subsequent osteoneogenesis is observed after obstruction of the labyrinthine artery. This arterial obstruction is generally not associated with endolymphatic hydrops of the cochlea.[51]
Osteoneogenesis is not only described in CS but also in other diseases as polyarteritis nodosa.[50]

Conclusions

1. Cogan's syndrome is a disease with its own identity.
2. As long as the actual causes of CS is unknown, it seems justified to distinguish two variants: TCS and ACS.
3. The presence of the typical ophthalmological signs and symptoms are obligatory for the diagnosis of CS.
4. The hearing loss is sensorineural and located in the cochlea.
5. The audiological threshold is often characterized by a fluctuating low-tone hearing loss, a 'cut-off frequency' in the audiometric curve, and an irriversable high-tone hearing loss.
6. Although no hard clues as to the pathogenic mechanism have been found, there is evidence that CS has an immunopathological substrate:
   - There are non-specific peripheral signs of inflammatory processes in a number of patients (elevated erythrocyte sedimentation rate and leukocytosis).
   - Specific immunological findings such as antibodies to inner ear and corneal tissue, and the presence of lymphocytes, macrophages, and plasma cell infiltrates in both the cornea and inner ear have been shown.
   - Response to systemically administered glucocorticoids is demonstrated, especially if treatment is started within one week after the onset of the syndrome.
   - There is a bilateral involvement of the eyes and audiovestibular organs.
   - Exacerbations and remissions of the ophthalmological and audiovestibular symptoms are common.

Recommendations

THERAPEUTIC

On the basis of this study, we recommend a high daily dosis (1 mg/kg) of systemic glucocorticoids in the initial phase of the syndrome. This dosage can be tapered off after one week, if complete recovery has taken place. Otherwise, we suggest continuing this dosage for a second week.
Based on our findings we recommend to add cytotoxic immunosuppressants (azathioprine): (1) in patients with an initial hearing loss of more than 60 dB, (2) if glucocorticoid therapy has not the expected result after 2 weeks, (3) after an exacerbation of the disease irrespective of earlier treatment with glucocorticoids, and (4) when it proves impossible to taper the glucocorticoid dosage without recurrence of the hearing loss. For each patient the toxic risks of glucocorticoid and azathioprine therapy have to be taken into account.
When CS has produced bilateral (sub)total deafness a cochlear implant should be considered without delay, as osteoneogenesis may hamper the introduction of electrodes.

FUTURE RESEARCH

If we accept the hypothesis that CS is an autoimmune disease, based on shared autoantigenic cross-reactivity in the eyes and ears, the following studies might be conducted in the future.

(1) Sera from CS patients could be studied with the Western blotting technique, using antigens from fresh eye and inner ear tissue.

(2) Sensitive lymphocyte transformation tests could be performed.

Both methods have proved to be useful adjuncts in studying rapidly progressive sensorineural hearing loss. Analysis of the autoantibody reactivity spectrum in Western blots of eye and ear extracts might demonstrate disease-specific autoantibodies. These observations could then be instrumental in difining (cross-reactive) antigens, which might further be defined by molecular techniques.

The prospects for the suggested studies are promising, especially because patient's serum is easily available and because it is not necessary to fix the fresh porcine eye and inner ear tissue.

(3) If post-mortem examination of a CS patient is possible, immunohistopathological investigations will be hampered as tissue processing involves fixation and decalcification, which impairs antigenic properties. In addition to these limitations the unavoidable delay in fixation of human inner ears will diminish antigenic properties too. Nevertheless, in case it is possible to perform a post-mortem investigation of the temporal bones of a CS patient, our post-mortem protocol should prove useful (see Addendum).

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SAMENVATTING

Samenvatting

HET SYNDROOM VAN COGAN

Het syndroom van Cogan (CS) is vernoemd naar de oogarts Cogan die in 1945 vier patiënten beschreef met "niet-syfilitische interstitiële keratitis (hoornvliesontsteking) gepaard gaande met draaiduizeligheid, oorsuizen *of* gehoorverlies." Enkele jaren later blijkt ook het gehoorverlies een obligaat verschijnsel te zijn van de aandoening.
De meeste patiënten zijn jong en hebben geen medische voorgeschiedenis. De ziekte ontwikkelt zich in een aantal dagen met een tweezijdige keratitis en een tweezijdig perceptief gehoorverlies. Tegelijkertijd ontstaat meestal draaiduizeligheid met misselijkheid, braken en oorsuizen. Vaak zijn er tevens vage algemene klachten zoals koorts, gewichtsverlies, moeheid en hoofdpijn met soms spierpijn, gewrichtspijn en vage bovenbuiksklachten.

DIFFERENTIAAL DIAGNOSE (TCS EN ACS)

In Hoofdstuk 2 wordt op basis van een uitgebreide literatuurstudie de differentiaal diagnose van CS belicht. Bij polyarteritis nodosa, relapsing polychondritis, M. Wegener, rheuma etc., kunnen elementen voorkomen die overeenkomsten vertonen met CS. Toch lijkt CS een zelfstandig ziektebeeld te zijn. Aan de hand van deze literatuurstudie is een werkdefinitie van CS geformuleerd.
De typische vorm van CS (TCS) wordt gekenmerkt door: (1) een tweezijdige focale, perifeer gelokaliseerde, interstitiële keratitis met of zonder conjunctivale hyperemie en ciliaire roodheid vaak gepaard gaande met exacerbaties en remissies; (2) een meestal tweezijdige perceptieve doofheid, oorsuizen en evenwichtsstoornissen; en (3) onbegrepen systemische klachten bij een blanco voorgeschiedenis wat betreft oog- en ooraandoeningen.
De atypische vorm van CS (ACS) is het bovenbeschreven syndroom in combinatie met een andere belangrijke oogontsteking naast de keratitis.

VASCULITIS EN/OF AUTO-IMMUUN STOORNIS

Door verschillende auteurs wordt aangenomen dat een vasculitis (vaatontsteking) of een auto-immuunziekte aan CS ten grondslag ligt. In Hoofdstuk 3 worden de in de literatuur beschreven histopathologische en immunologische bevindingen besproken. Alhoewel bij CS in verschillende organen een vasculitis is gevonden, is deze nooit aangetoond in het oog of het oor. Het is daarom de vraag of een vasculitis de "oorzaak" van CS is of dat er sprake is van een epiphenomeen.
Een auto-immuun proces lijkt waarschijnlijk. Aspecifieke tekenen van ontsteking zoals verhoogde bezinking en leukocytose werden frequent gezien en bij enkele patiënten werden specifieke immunologische afwijkingen gevonden. Bovendien pleit

het positieve therapeutische effect van glucocorticoïden voor deze pathogenese. Indien CS een auto-immuunziekte is betreft het waarschijnlijk een locale reactie in het oog en het oor en zou een gemeenschappelijke auto-antistof-kruisreactiviteit in het oog en het oor in dit proces betrokken kunnen zijn.

WESTEUROPESE STUDIE

In de Hoofdstukken 4 en 5 worden de resultaten van een retrospectieve West-europese CS studie beschreven. De klinische gegevens werden geanalyseerd van 98 patiënten met de veronderstelde diagnose CS, behandeld tussen 1968 en 1993 in 10 verschillende landen. De patiëntengroep bestond uit 37 patiënten met TCS en 22 met ACS. De overige 39 voldeden niet aan eerder genoemde criteria. Met 59 ingesloten patiënten is dit de grootste groep die ooit is onderzocht.

OOGVERSCHIJNSELEN

Bij 35 TCS and 21 ACS patiënten werd een tweezijdige en bij 3 (2 TCS, 1 ACS) patiënten een enkelzijdige interstitiële keratitis gevonden. De oogklachten gingen vaak gepaard met exacerbaties en remissies maar dit werd helaas niet altijd beschreven. Dit komt waarschijnlijk door de goede reacties op glucocorticoïden en omdat het oogbeeld bij deze vaak zeer zieke patiënten minder opvallend is.

GEHOORVERLIES

Behalve 1 ACS patiënt die een unilateraal gehoorverlies had, ontwikkelden alle andere patiënten een bilateraal perceptief gehoorverlies. Aangezien recruitmenttesten positief waren en retrocochleaire pathologie (indien getest) werd uitgesloten, is het gehoorverlies waarschijnlijk van cochleaire (het slakkenhuis betreffende) aard. Deze conclusie werd nog eens bevestigd door de afwijkingen welke in het binnenoor werden gezien met behulp van CT en MRI (zie Hoofdstuk 8).
Oorsuizen was bij een groot aantal (84%) patiënten aanwezig, terwijl bovendien bijna eenderde klaagde over drukgevoel in beide oren.
Bij de meeste patiënten met een licht of matig gehoorverlies werd een scherpe knik (afsnij-frequentie) in het audiogram, meestal tussen 1000 en 2000 Hz gevonden. Dit typische beloop van het gehoorverlies is niet eerder beschreven. In de literatuur wordt gesuggereerd dat er twee systemen onderscheiden kunnen worden in de cochlea, één voor de lage en één voor de hoge frequenties, waardoor voornoemde knik verklaard zou kunnen worden.
Bij de meeste patiënten bleek het perceptieve gehoorverlies, met name in de lage frequenties te fluctueren, soms spontaan, soms in relatie met de gegeven therapie. Omdat veel patiënten klaagden over een druk gevoel in het oor en een endolym-

fatische hydrops in obductierapporten wordt beschreven zou het mogelijk kunnen zijn dat een wisselende endolymfatische hydrops (deels) een oorzaak van de fluctuaties is.
Bij patiënten met een licht tot matig gehoorverlies werd in een aantal gevallen aanzienlijke verbetering tot (sub)totaal herstel bereikt. In bijna alle gevallen resteerde echter een hoge-tonen verlies. Van geen van de patiënten met een gehoorverlies voor therapie van 60 dB of meer herstelde het gehoor. Een mogelijke verklaring hiervoor zou zijn dat de buitenste haarcellen grotendeels irreversibel zijn gedegenereerd.

EVENWICHTSSTOORNIS

Behalve 1 ACS-patiënt hadden alle patiënten evenwichtsklachten, welke varieerden van draaiduizeligheid tot een onzeker gevoel bij het lopen. Bij bijna allen werd een calorisch onderzoek verricht dat bij eenderde een volledige uitval liet zien. Bij 1 TCS- en 3 ACS-patiënten werden geen afwijkingen gevonden. Alle patiënten met een uitval klaagden over instabiliteit in de eindfase met name bij snelle hoofdbewegingen en in het donker.

ALGEMENE BEVINDINGEN

Behalve de eerder besproken symptomen van algemene malaise werd bij 43% TCS- en 27% ACS-patiënten kort voor het begin van het CS een bovenste luchtweginfectie geconstateerd. Pogingen om een micro-organisme te vinden leverden zelden resultaat op.
Een bijzondere bevinding was de testiculaire pijn waarover 2 van de 4 patiënten die door de auteur zelf behandeld zijn, klaagden. Een testis biopt liet geen afwijkingen zien, met name geen vasculitis. Bij de overige 28 mannen die participeerden in dit onderzoek werd dit verschijnsel slechts eenmaal vermeld.
Ondanks dat vaak gesuggereerd is dat CS een uitingsvorm is van een bekende systeemziekte, zoals bijvoorbeeld polyarteritis nodosa of relapsing polychondritis, hebben wij bij de 59 onderzochte patiënten hiervoor geen aanwijzingen gevonden. In Hoofdstuk 7 wordt ter illustratie hiervan een patiënt besproken met een histopathologisch bewezen relapsing polychondritis, bilateraal perceptief gehoorverlies, oorsuizen , duizeligheid en corneaal oedeem met guttata, ciliaire, conjunctivale en episclerale hyperemie in het rechter oog. Alhoewel geen interstitiële keratitis werd gevonden waren de overeenkomsten met ACS opvallend.

LABORATORIUMBEVINDINGEN

Algemene laboratoriumgegevens leverden in onze studie weinig op. Meestal wordt een verhoogde bezinking en leukocytose gevonden. De rest van de laborato-

riumuitslagen zijn over het algemeen volledig normaal. Dit is merkwaardig omdat in een normaalpopulatie ook kleine afwijkingen van het bloedbeeld kunnen worden verwacht. Een mogelijke verklaring hiervoor zouden de relatief jonge leeftijd en de blanco voorgeschiedenis van de patiënten kunnen zijn.
Immunologisch onderzoek was eveneens negatief. Dit maakt de hypothese dat een eventuele auto-immuunreactie locaal (oog en oor) plaats zou vinden meer aannemelijk. De lichte verhoging van de bezinking en acuut-fase-eiwitten zouden kunnen wijzen op een onderliggende locale ontstekingsreactie, eventueel geïnduceerd door een autoimmuunreactie.

Cornea antilichamen
In Hoofdstuk 6 is verslag gedaan van een onderzoek naar de aanwezigheid van cornea antilichamen bij 1 TCS- en 1 ACS-patiënt. Bij beide patiënten werden deze antilichamen gevonden bij het begin van CS of tijdens een exacerbatie van de ziekte, en niet tijdens of na therapie met glucocorticoïden. Antilichamen tegen (onderdelen van) de cornea werden behalve in de eerder beschreven patiënt met relapsing polychondritis (Hoofdstuk 7) ook beschreven in andere oogheelkundige ziektebeelden zodat deze niet specifiek voor CS genoemd mogen worden.

LABYRINT AFWIJKINGEN: EEN CT EN MRI ONDERZOEK

In Hoofdstuk 8 werd een geavanceerde radiodiagnostische techniek beschreven welke bestaat uit een combinatie van CT en MRI, waardoor het mogelijk is kleine pathologische structuren in het labyrint (binnenoor) zichtbaar te maken.
Bij 4 patiënten werd een vernauwing of zelfs volledige obstructie van weke delen van de halfcirkelvormige kanalen gevonden. Deze afwijkingen waren in overeenstemming met de klachten en afwijkingen zoals uitval bij calorische stimulatie.
Bij 3 patiënten werden weke delen gevonden in de basale en secundaire winding van de cochlea. Deze bevindingen kwamen overeen met het prominente hoge-tonen verlies bij deze patiënten ten tijde van het radiologisch onderzoek. Naast accumulaties van weke delen werd botnieuwvorming gezien bij 1 patiënt.
Met de contrastvloeistof Gadolinium konden met de MRI T1-gewogen opnamen worden gemaakt waarbij dubbelzijdige aankleuring van de cochlea en het vestibulum werd gezien. Dit zou kunnen passen bij een actief proces zoals vasculitis of ontsteking.
Bij 1 patiënt, die volledig herstelde zonder enig gehoorverlies, werden geen afwijkingen gevonden.

EFFECT VAN GLUCOCORTICOID THERAPIE

De oogafwijkingen herstelden bij de meerderheid van de patiënten volledig binnen twee weken. Het herstel was onafhankelijk van het feit of locaal of systemisch

glucocorticoiden werden toegediend.
Herstel c.q. aanzienlijke verbetering van het gehoor deed zich alleen voor indien spoedig na het begin van de ziekte patiënten met glucocorticoïden werd behandeld. Zo herstelden alle 7 patiënten bij wie binnen één week gestart werd met de medicatie, en 2 van de 6 patiënten bij wie de behandeling begon na 1 week maar niet later dan na 2 weken. Bij een langer interval was het effect nihil (Hoofdstuk 5). Herstel van het gehoor vond verder alleen plaats indien hoge doses glucocorticoïden (1 mg/kg/dag) werden toegediend.

EFFECT VAN CYTOSTATICA

De rol van cytostatica zoals cyclofosfamide en azathioprine, is vooralsnog niet duidelijk. Doordat in bijna alle gevallen glucocorticoïden werden gegeven is beoordeling van het effect van andere additioneel gegeven therapieën moeilijk. Omdat cytostatica bekend zijn om hun ernstige bijwerkingen (beenmergdepressie, teratogeniciteit, azoöspermie, etc.) is een terughoudend beleid gewenst.
Door ons werden vijf patiënten behandeld met azathioprine. Soms als ondersteunende therapie bij het uitsluipen van de glucocorticoïden indien dit laatste gepaard ging met toenemend gehoorverlies, en als aanvullende therapie naast glucocorticoïden tijdens een recidief van de ziekte. Bij 1 patiënt verslechterde het gehoor, bij 3 patiënten stabiliseerde het verlies en bij 1 patiënt herstelde het gehoor volledig.
Gezien het complementaire effect van cytostatica (op glucocorticoïden) en hun betekenis bij behandeling van immunologisch geïnduceerde ziekten, moeten cytostatica overwogen worden: (1) bij de prognostisch slechte patiëntengroep met een gehoorverlies groter dan 60 dB; (2) indien na twee weken de initiële glucocorticoïd-therapie onvoldoende effect heeft; (3) bij een exacerbatie van de ziekte en; (4) wanneer het onmogelijk is de glucocorticosteroïden uit te sluipen. Echter tijdens de therapeutische besluitvorming zullen voor elk individueel geval het te verwachten therapeutisch effect en de bijwerkingen van zowel glucocorticoïden als cytostatica tegen elkaar afgewogen moeten worden.

CONCLUSIES

1. Het syndroom van Cogan is een zelfstandig ziektebeeld.
2. Zolang de oorzaak van het syndroom van Cogan onbekend is lijkt het gerechtvaardigd een onderscheid te maken tussen TCS en ACS.
3. Het typische oogbeeld blijkt van grote waarde te zijn bij het stellen van de diagnose.
4. Het gehoorverlies is perceptief en in de cochlea gelocaliseerd.
5. Het audiogram wordt gekarakteriseerd door een voornamelijk in de lage-tonen fluctuerend verlies, een afsnij-frequentie en een irreversibel hoge-tonen verlies.

6. Alhoewel een algemeen immunologisch onderzoek over het algemeen negatief was, zijn er toch aanwijzingen voor een oorzakelijk immunologisch lijden:
   - lichte stijging van de bezinking en de acuut-fase-eiwitten eventueel passend bij een locale ontstekingsreactie;
   - specifiek immunologische bevindingen zoals antilichamen tegen onderdelen van de cornea en het binnenoor, en de in de obductierapporten beschreven celinfiltraten bestaande uit lymfocyten, macrofagen en plasmacellen in het hoornvlies en het binnenoor;
   - goede reacties op glucorticoïden in het begin van de ziekte;
   - betrokkenheid van meestal beide ogen en oren in het proces;
   - het fluctuerende beloop van zowel de oogklachten als de audiovestibulaire klachten.

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Curriculum vitae

Maarten Majoor werd op 7 december 1957 geboren te Nijmegen. In 1976 behaalde hij het HAVO-examen en in 1978 het diploma Atheneum-B, aan de Scholengemeenschap Canisius College-Mater Dei. Hierna vervulde hij de militaire dienstplicht.
In 1979 begon hij met de studie geneeskunde aan de Universiteit van Amsterdam. Tijdens zijn studie was hij kandidaat-assistent anatomie. Tevens werd experimenteel onderzoek verricht naar hepatogene encefalopathie bij de Afdeling Experimentele Inwendige Geneeskunde (Prof. Dr.. J. van Gool) en naar het neuroblastoom bij kinderen, bij de Afdeling Kindergeneeskunde (Prof. Dr.. P.A. Voûte), Academisch Medisch Centrum Amsterdam. In 1987 behaalde hij het artsexamen cum laude.
Vanaf april 1988 was hij in opleiding tot Keel-, Neus- en Oorarts in het Academisch Ziekenhuis Utrecht (opleiders: Prof. Dr.. E.H. Huizing en Prof. Dr.. G.J. Hordijk). De opleiding werd in april 1993 voltooid. Tijdens de opleiding was het mogelijk aan het onderzoek te werken dat heeft geresulteerd in dit proefschrift.
Op dit moment is hij als Keel-, Neus- en Oorarts verbonden aan het Academisch Ziekenhuis te Utrecht.
De auteur is getrouwd met Mègy van Wijck. Zij hebben drie kinderen: Bas, Juleke en Tijn.

ADDENDUM

1- Cogan's syndrome data file used in this study
2- Diagnostic recommendations
3- Protocol for post-mortem immunopathology of temporal bones from patients with Cogan's syndrome

Cogan's syndrome data file used in this study

INDEX

CS = Cogan's syndrome (TCS is typical; ACS is atypical)
Y/N = Yes/No
stationary phase = phase of the syndrome in which the patient has recovered from his systemic and eye complaints and has a stable hearing loss without fluctuations.

tympanometry classification:
type A = middle ear pressure < -100 mm H_2O
C1 = middle ear pressure of -100 to -200 mm H_2O
C2 = middle ear pressure > -200 mm H_2O
B = compliance below 0.25 ml

PATIENT DATA

name	:	specialism	:
first name(s)	:	name specialist	:
date of birth	:	department	:
male/female	:	address	:
marital status	:	tel	:
occupation	:	country	:
address/tel	:		
country	:		

GENERAL HISTORY

			date
date first symptoms	:		
age first symptoms	:		
initial eye involvement	: Y/N	R/L	
initial ear involvement	: Y/N	R/L	
simultaneous eye/ear involvement	: Y/N		
interval between eye/ear involvement	:	days	
duration of disease (start of initial symptoms until stationary phase; see index).	:	days/wks	
follow-up	:	days/wks	
infection : - before first symptoms	: Y/N		
- interval infection-symptoms	:	days	
type of infection : - localization	:		
- micro-organism	:		
vaccination	:		
fever	: Y/N	°C	
weightloss	: Y/N	Kg	
fatigue	: Y/N		
other symptoms	:		

PAST HISTORY

- eyedisease :
- diabetes :
- thyroid disease :
- trauma :
- surgery :
- medication before first symptoms :
- ear disease :
- kidney disease :
- autoimmune disease :
- intoxication :
- other :
- nicotine abusis :
- alcohol abusis :

HISTORY

Eye date

- unilateral, bilateral : uni/bi
- redness : Y/N
- photophobia : Y/N
- eye discomfort : Y/N
- diplopia : Y/N
- exacerbations and remissions : Y/N
- contact lenses : Y/N
- work/living in airconditioned space : Y/N

general ophthalmological history

- normal : Y/N
- salient findings :

Ear date

- hearing loss before CS : Y/N
  (if available, enclose audiogram)
- initial hearing loss: - unilateral : L/R
  - bilateral : Y/N
- interval unilateral-bilateral hearing loss : days
- interval vertigo-hearing loss : days
- noise exposure : Y/N
- tinnitus : Y/N
- tinnitus with temporal pain : Y/N
- fullness in the ears : Y/N
- otorrhea : Y/N
- otalgia : Y/N

general ORL history

- normal : Y/N
- salient findings :

Equilibrium date

- vertigo : Y/N
- dysbalance : Y/N
- vertigo attacks :
- vegetative reactions : Y/N

Head and neck date

- headache : Y/N
- poorly localized discomfort : Y/N
- periorbital pain : Y/N
- postauricular pain : Y/N

Further symptoms date

Nervous system
- general :

Musculskeletal date
- arthritis :
- arthralgia :
- myalgia :
- other :

Abdominal date
- discomfort :
- hemorrhage :
- other :

Lymphoreticular : date
- lymphadenopathy :
- splenomegaly :
- hepatomegaly :

Pulmonary date
- dyspnea :
- pleuritis :
- other :

Cardiac date
- dyspnea :
- other :

Urogenital date
- testicular pain :
- other :

Dermatological date
- symptoms :

Psychological date
- symptoms :
- stress :
- depression :

EXAMINATION

Ophthalmologic; first examination date

- interstitial keratitis (diffuse midstromal) : Y/N
- diffuse episcleral injection : Y/N
- deep corneal vascularization : Y/N
- excess lacrimation : Y/N
- ciliar flush : Y/N
- episcleritis : Y/N
- inflamed optic papilla : Y/N
- papilledema : Y/N
- cells anterior chamber : Y/N
- sensibility cornea normal : Y/N
- visual fields :
- opacity near the limbus : Y/N
- corneal opacity (evanescent) : Y/N
- hyperaemic perilimbal vessels : Y/N
- conjunctival hyperaemia : Y/N
- pus/mucus : Y/N
- uveitis : Y/N
- scleritis : Y/N
- macular involvement : Y/N
- thin sclera : Y/N
- corneal ulceration : Y/N
- visual acuity :
- other findings :

Final examination at stationary phase date
- blindness : Y/N
- visual fields :
- visual acuity :
- persisting symptoms :

ORL; first examination date

Otological:	- normal	: Y/N	Rhinological:	- normal	: Y/N
	- abnormal	:		- abnormal	:
Laryngological:	- normal	: Y/N	Head and neck	- normal	: Y/N
	- abnormal	:		- abnormal	:

Final examination at stationary phase date
- persisting symptoms :
- salient findings :

Neurological; first examination date

- peripheral nerve involvement	:	- cranial neuropathy	:
- mononeuritis multiplex	:	- meningismus	:
- encephalitis	:	- other findings	:

Final examination at stationary phase date

- other symptoms	:	- salient findings	:

Musculskeletal; first examination date

- arthritis	:	- myositis	:
- polychondritis	:		

Final examination at stationary phase date

- other symptoms	:	- salient findings	:

Abdominal; first examination date

- hemorrhage	:	- other findings	:

Final examination at stationary phase date

- other symptoms	:	- salient findings	:

Cardiac; first examination date

- tachycardy	:	- systolic murmur	:
- aortic insufficiency	:	- left ventricular hypertrophy	:
- other findings	:		

Final examination at stationary phase date

- other symptoms	:	- salient findings	:

Pulmonary; first examination date

- abnormalities	:	- pleuritis	:

Final examination at stationary phase date

- other symptoms	:	- salient findings	:

Cutaneous; first examination date

- nodules	:	- rash	:

Final examination at stationary phase date

- other symptoms	:	- salient findings	:

Lymphoreticular first examination date

- lymphadenopathy :
- splenomegaly :
- hepatomegaly :
- other findings :

Final examination at stationary phase date

- other symptoms :
- salient findings :

Psychological; first examination date

- symptoms :

Final examination at stationary phase date

- other symptoms :
- salient findings :

Other; first examination date

- symptoms :

Final examination at stationary phase date

- other symptoms :
- salient findings :

AUDIOMETRY

1. Audiometry during initial phase date

Pure tone audiometry

L			R		
250 Hz	:	dB (HL)	250 Hz	:	dB (HL)
500	:		500	:	
1000	:		1000	:	
2000	:		2000	:	
4000	:		4000	:	
8000	:		8000	:	

(audiometers calibrated according to ISO 1964 standard, Hearing Level).

- air bone gap (≥ 10 dB) : Y/N
- tinnitus analysis :

Speech audiometry

- maximum discrimination : %
- phoneme regression : Y/N
- 50% speech level : dB(SPL)

Tuning fork test

- Rinne : +/- R +/- L
- Weber lateralization (if yes R/L) : Y/N

Recruitment test : Y/N

Tone decay test

- tone decay ≥ 30 dB : Y/N
- tone decay, varying : Y/N

Békésy (Jerger)

- Békésy excursions small : Y/N
- choose Békésy 1,2,3, or 4 : Y/N

Stapedial reflex, ipsi/contra-lateral

- probe R : Y/N
- probe L : Y/N

Glycerol test (Klockhoff/Lindblom)
- improvement ≥ 10 dB : Y/N

Tympanometry
- normal : Y/N
- if N, fill in classification : R L (A, B, C1, or C2; see Index)

2. *Audiometry during stationary phase* date

Pure tone audiometry

L	250 Hz :	dB (HL)	R	250 Hz :	dB (HL)
	500 :			500 :	
	1000 :			1000 :	
	2000 :			2000 :	
	4000 :			4000 :	
	8000 :			8000 :	

(audiometers calibrated according to ISO 1964 standard, Hearing Level).

- air bone gap (≥ 10 dB) : Y/N
- tinnitus analysis :

Speech audiometry
- maximum discrimination : %
- phoneme regression : Y/N
- 50% speech level : dB(SPL)

Tuning fork test
- Rinne : +/- R +/- L
- Weber lateralization (if yes R/L) : Y/N

Recruitment test : Y/N

Tone decay test
- tone decay ≥ 30 dB : Y/N
- tone decay, varying : Y/N

Békésy (Jerger)
- Békésy excursions small : Y/N
- choose Békésy 1,2,3, or 4 : Y/N

Stapedial reflex, ipsi/contra-lateral
- probe R : Y/N
- probe L : Y/N

Glycerol test (Klockhoff/Lindblom)
- improvement ≥ 10 dB : Y/N

Tympanometry
- normal : Y/N
- if N, fill in classification : R L (A, B, C1, or C2; see Index)

ENG

date

Vestibulo-spinal reflexes

- Romberg test : +/- to the R\L below norm
- Gait test : +/- to the R\L below norm

Spontaneous nystagmus

- nystagmus : Y/N to the R\L ..... o/sec
  - rotatory - clockwise
  - counterclockwise

Positional nystagmus

- nystagmus : Y/N to the R\L ..... o/sec

Caloric response

- nystagmus : Y/N
  - canal paresis (unilateral weakness) .... %
  - directional preponderance .... %

Rotating chair test

- response : Y/N
- hypo-response : Y/N

LABORATORY

date

General

- ESR : mm/h
- HB : mmol/l
- MCHC : mmol/l
- MCH : amol
- MCV : fl
- WBC : 10/cu mm
  - eosinophils : %
  - neutrophils : %
  - lymphocytes : %

Electrolytes date

- normal : Y/N (if not, provide further details)

Liver / Kidney date

- urea : mmol/l
- creatinine : µmol/l
- alkaline phosphatase : U/l
- ASAT (GOT) : U/l
- ALAT (GPT) : U/l
- LD : U/l
- glucose : mmol/l

Serum proteins date

- electrophoresis : normal, Y/N
  - if no,specify :
- albumin : gm/100ml
  - fibrinogen : gm/100ml
- paraproteins : Y/N
  - if yes, specify :
- other findings :

Spinal fluid date

- protein total : mg/100ml
  - globulins :
- electrophoresis :
  - white cells :
- red cells :
  - glucose :

Urine analysis :

IMMUNOLOGY (state methods) date

Immunoglobulins

- IgM :
- IgA :
- IgD :
- IgG :
- IgE :

Complement (g/l or U/ml) date

- C3 :
- C1q :
- CH50 :
- C4 :
- C3d, C3a, C5a :

Autoantibodies

- thyroid :
- parietal cells :
- nuclear :
  (ANA, LE test, including ENA test)
- stomach :
- pancreas :
- rheumatoid :
- other :

date

Blood leukocyte function / phenotyping date

- lymphocyte func. tests:
- lymphocyte phenotyp.:
- other :

HLA typing date

- HLA - B27 :
- other :
- Bw35 :

Other immunological investigations
e.g. circulating immune complexes

ALLERGY TESTS

date

- skin test :
- provocation test :
- IgE; see Immunology
- RAST test :
- other :

ELECTROGRAPHY

- EEG :
- ECG :
- EMG :

RADIOLOGY

- X- chest :
- X- Stenvers :
  NMR :
  Angiography :
  Computerized Tomography
- os petrosum :
- X- sinus :
- X- Schüller :
- other :

SCREENING OF INFECTION date

Serology (type of test, titers)

- bacteriology	: Y/N	- virology	: Y/N
-syphilis	: Y/N	- chlamydia	: Y/N
- mycology	: Y/N	- parasitology	: Y/N

date

Cultures (type of test, virus, bacteria)

- eyes	: Y/N	- ears	: Y/N
- sputum	: Y/N	- serum	: Y/N
- spinal fluid	: Y/N	- feces	: Y/N
- urine	: Y/N		

PATHOLOGICAL ANATOMY (enclose autopsy report)

Biopsy

Histology results		Immunohistopathology results	
- skin	: Y/N	- skin	: Y/N
- fascia	: Y/N	- fascia	: Y/N
- muscle	: Y/N	- muscle	: Y/N
- other	:	- other	:

Revision by us possible? Frozen and/or paraffin biopsy material available?

Autopsy (enclose autopsy report)

Autopsy	: Y/N
- trepanation	: Y/N
- petrous bone:	
- histology	: Y/N
- immunohistopathology	: Y/N

Revision by us possible? Frozen and/or paraffin biopsy material available?

FOLLOW-UP

Treatment

Systemic medication

	Medicament	Dosage	Duration	Date
1.	.....	.....	.....	.....
2.	.....	.....	.....	.....
3.	.....	.....	.....	.....

Local medication

	Medicament	Dosage	Duration	Date
1.	.....	.....	.....	.....
2.	.....	.....	.....	.....
3.	.....	.....	.....	.....

Relevant findings between initial and stationary phase of the syndrome

Physical symptoms

- Ear
- Equilibrium
- Eye
- Head and neck
- Other

Audiometry, If available please enclose relevant data (e.g. pure tone and speech audiograms)

ENG

Laboratory

Special tests

Diagnostic recommendations

- Diagnostic examinations should include a thorough patients history, followed by detailed ophthalmological, otological and physical examination. Other specialists will be consulted depending on the symptomatology.
- Repeated audiometry is recommended, because of its importance in monitoring treatment. Tympanometry, and stapedius reflextest ard Békésy recruitment tests are advised.
- Vestibular function tests should include electronystagmography, examination of vestibulo-spinal reflexes, and, if possible, rotating chair nystagmography.
- General serological tests have to be conducted (ESR, WBC, glucose, thyroid function, etc).
  It is imperative to perform a general immunological survey ((serum immunoglobulins, CRP, autoantibodies (to cornea and ear, ANCA, ACE, LE-cell test, rheumatoid factor, ANA), circulating autoimmune complexes, and a full complement profile).
  Serological tests for syphilis are essential. Tests for herpes, rubella, mumps, influenza and tuberculin skin tests are recommended.
- Occasionally, echocardiograms will be needed if aortic insufficiency is suspected; biopsies of cutaneous lesions should be taken.
- Radiological examination (chest, sinus, abdomen, including visceral or cerebral angiography for the evaluation of systemic vasculitis) and other specific radiological techniques (technetium scans) have to be done on indication. When possible, computed tomography and magnetic resonance imaging of the temporal bones have to be carried out.

Protocol for post-mortem immunohistopathology of temporal bones from patients with cogan's syndrome

INTRODUCTION

This manual is based on the report "Functional Histopathology of the Human Audiovestibular Organ" by the Commission of the European Communities, Luxembourg 1982.[1,2]
Investigation of the inner ear is performed by two different techniques:

- Right ear : transmission electron microscopy (TEM)
- Left ear : Immunopathology

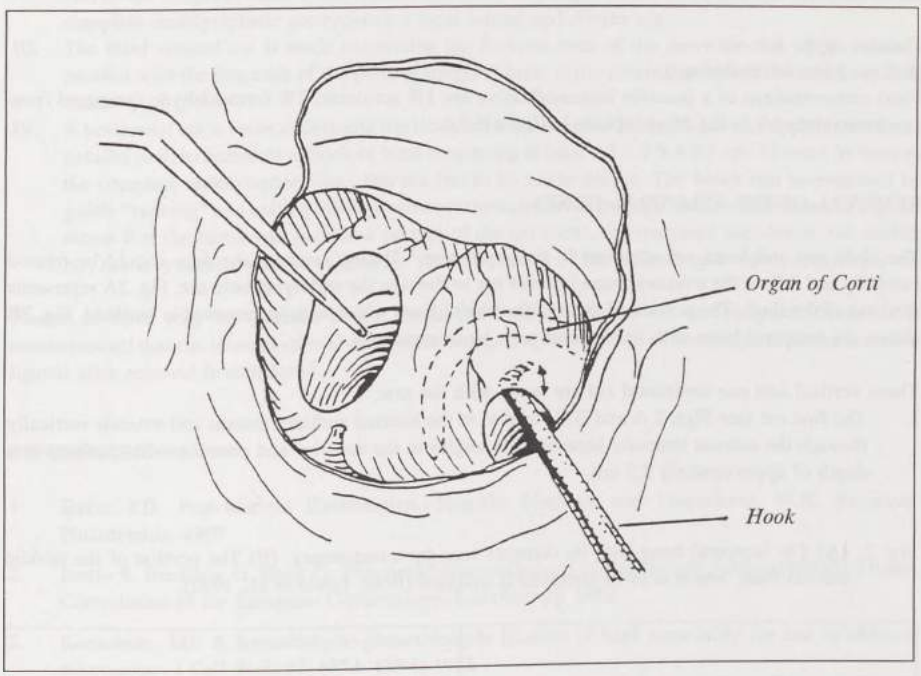
PROTOCOL

1. Obtain approval for autopsy of patient's brain.
2. Inform one of the members of the Study Group: European Study of Cogan's Syndrome, Department of Otorhinolaryngology, University Hospital Utrecht, The Netherlands.
   - Dr. MHJM Majoor tel: (31)30509111 tracer: 1466
   - Prof. Dr. EH Huizing tel: (31)30506645
3. Perform a perilymphatic perfusion of both temporal bones and remove the temporal bones as described below.
   If you wish, we can carry out the perilymphatic perfusion for you. We can come to your clinic immediately with the necessary equipment.
   To minimize post-mortem autolysis, the perilymphatic space has to be perfused immediately after death.
4. Complete:
   - Cogan's syndrome data file
   - Interval between death and fixation: ..... hours
5. One of the members of our group will visit you and collect the temporal bones along with the Cogan's syndrome data file.

PERILYMPHATIC PERFUSION

Immediately following death, the perilymphatic space is perfused through an endaural approach. A microscope with 6-10 times magnification is necessary for the procedure, which is essentially that of stapedectomy.
Using an ear speculum, the upper posterior part of the tympanic membrane is folded forward. With a chisel, the bony overhang is removed in order to expose the oval and round windows. The incudostapedial joint is divided, and the stapes is luxated from the window. The round window is perforated with a small hook (120° and 0.50 mm long) directed forward (in the direction of the Eustachian tube; Fig. 1). This is a crucial step in the procedure. Be certain that the membrane is really perforated. Often there may be extra membranes in the window niche. Be careful to direct the surgical hook forward (not towards the oval window) to avoid damaging the osseus spiral lamina or *the organ of Corti* in the round window region.
Damage to the osseous spiral lamina in this region creates a shunt between the two windows and prevents the fixative from circulating within the cochlea (above approx. 5 mm), thus resulting in insufficient preservation of its major portion.
A subsequent step is the actual perilymphatic perfusion. A syringe with an unsharpened needle (tip diameter 0.5-1.0 mm) is filled by aspiration with 1-2 ml of fixing solution (see Preparation of the Fixative) at room temperature. The tip is directed toward the oval window, and the fixative is infused. Be careful to observe that fluid is really flowing out of the oval window, indicating complete perfusion

Fig. 1 Perilymphatic perfusion (from: Iurato et al., 1982).



of scala vestibuli and tympani. When the fixative has been infused (be careful to prevent any air bubbles from entering the labyrinth), aspirate carefully in the region of the round window so that excess fixative is removed and poured in a waste jar. Repeat the procedure with fresh fixative and aspirate again. In this way the perilymphatic spaces are perfused for 15 minutes (at least 10 times).

It is very important to check that fluid is actually flowing out of the round window. If not, try again to perforate the membrane. Take care also that air bubbles do not enter the labyrinth, either upon infusion through the oval window or upon aspiration from the round window. Air bubbles block further penetration and may cause mechanical distortion of the soft tissues inside the labyrinth.
After 15 minutes of perfusion, the middle ear is filled with cotton or filter paper soaked in fixative to prevent the fixative from leaking out into the ear canal, the Eustachian tube or into the mastoid cavity. The temporal bones are removed at autopsy according to the procedure discribed below. After the temporal bones have been removed, they should be immersed into the fixative and stored in the refrigerator at 4°C until delivery.

PREPARATION OF THE FIXATIVE

Half-strength Karnovsky[3]
(right ear/transmission electron microscopy)
To 80 ml of 0.4 M cacodylate buffer (pH 7.4), 40 ml of 16% formaldehyde (prepared from paraformaldehyde) and 40 ml of 8% glutaraldehyde are added. The resulting stock solution contains 4% formaldehyde, 2% glutaraldehyde in 0.2 M sodium cacodylate buffer.
To 120 ml of this stock solution 120 ml of distilled water containing 60 mg $CaCl_2$ are added. The final concentrations of the fixative are 2% formaldehyde, 1% glutaraldehyde, 0.1 M cacodylate buffer, 0.025%

$CaCl_2$. While the stock solutions can be kept in the refrigerator for several months, the final solution must be used within 3-4 weeks.

Fixative of the left ear
(left ear / immunopathology)
Final concentrations of a possible immunofixative are 1% acroleine, 2% formaldehyde (prepared from paraformaldehyde) in 0.1 M phosphate buffer, pH 7.4.

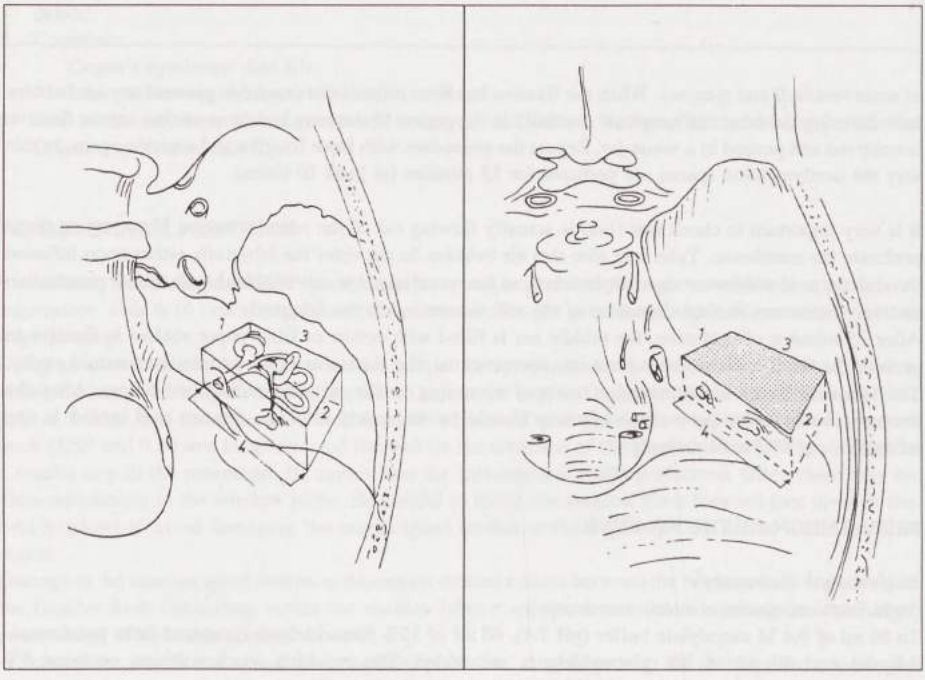
REMOVAL OF THE TEMPORAL BONES

The skull cap and brain are removed in the usual way.[4] During removal the dura should be treated carefully and left on the temporal bone in order not to damage the endolymphatic sac. Fig. 2A represents the base of the skull. The portion of the middle cranial fossa which is to be removed is outlined. Fig. 2B shows the temporal bone with its contents seen by transparency.

Three vertical and one horizontal cut are made with the saw.

I. The first cut (see Figs. 2 A and B) is medial to the internal auditory meatus and extends vertically through the petrous temporal bone at right angles to the superior and posteromedial surfaces to a depth of approximately 2.5 cm.

Fig. 2 (A) The temporal bone with its contents seen by transparency. (B) The portion of the middle cranial fossa which is to be removed is outlined (from: Iurato et al., 1982).



A B

II. The second cut is made parallel to the first and at least 2.5-3 cm posterolateral to it at the lateral end of the temporal bone. It also passes vertically to a depth of 2.5 cm. Note that removal of the complete endolymphatic sac requires a more lateral and deeper cut.

III. The third vertical cut is made connecting the forward ends of the previous cuts, approximately parallel with the free ends of the petrous temporal bone at the anterior extent of the middle cranial fossa.

IV. A horizontal cut is made underneath the temporal bone at about 2.5 cm below the upper surface and parallel to it, to complete a block of bone measuring at least 2.5 × 2.5 × 2.5 cm. In order to remove the complete endolymphatic sac, this cut has to be made deeper. The block can be removed by gently "rocking" and cutting the ligamentous structures on its inferior surface. Reference to Fig. 2B shows that the block will include a portion of the ear canal, the tympanic membrane, the middle ear, the labyrinthine structures, and the petrous portion of the seventh and eighth cranial nerves.

Plaster of Paris may be inserted in the space previously occupied by the temporal bones. It is recommended that the internal carotid arteries be clamped upon removal of the temporal bones and then ligated after removal is completed.

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